

From the: INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

AOYAMA, Tamotsu et al. Aoyama & Partners IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi Osaka 540-0001 JAPON



PCT

WRITTEN OPINION

(PCT Rule 66)

		Date of mailing (day/month/year)	02.05.2000
Applicant's or agent's file reference 661102		REPLY DUE	within 3 month(s) from the above date of mailing
International application No. PCT/JP99/03929	International filing date (d 22/07/1999		Priority date (day/month/year) 24/07/1998
International Patent Classification (IPC) or bot C12N15/12	h national classification and	I IPC	
Applicant SAGAMI CHEMICAL RESEARCH CI	ENTER et al.		

1. This written opinion is the first drawn up by this International Preliminary Examining Authority. 2. This opinion contains indications relating to the following items: 1 Basis of the opinion ☐ Priority Non-establishment of opinion with regard to novelty, inventive step and industrial applicability Ш IV ☐ Lack of unity of invention Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI Certain document cited ☐ Certain defects in the international application VII VIII Certain observations on the international application 3. The applicant is hereby invited to reply to this opinion. See the time limit indicated above. The applicant may, before the expiration of that time limit, When? request this Authority to grant an extension, see Rule 66.2(d) By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. How? For the form and the language of the amendments, see Rules 66.8 and 66.9. Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6. If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

Name and mailing address of the international preliminary examining authority:



European Patent Office D-80298 Munich

Tel. +49 89 2399 - 0 Tx: 523656 epmu d

The final date by which the international preliminary

examination report must be established according to Rule 69.2 is: 24/11/2000.

Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Vollbach, S

Formalities officer (incl. extension of time limits)

Vullo, C

Telephone No. +49 89 2399 8061





WRITTEN OPINION

International application No. PCT/JP99/03929

I.	Bas	is o	f th	ne o	pini	on

 This opinion has been drawn on the basis of (substitute sheets which have been furnished to the receivir in response to an invitation under Article 14 are referred to in this opinion as "originally filed".): 										
	Description, pages:									
	1-1	21	as originally filed							
	Cla	ims, No.:								
	1-6		as originally filed							
	Dra	awings, sheets:								
	1/5	0-50/50	as originally filed							
2.	The	amendments have	e resulted in the cancellation of:							
		the description,	pages:							
		the claims,	Nos.:							
		the drawings,	sheets:							
3.	This con	s opinion has been sidered to go beyor	established as if (some of) the amendments had not been made, since they have been not the disclosure as filed (Rule 70.2(c)):							
4.	Add	litional observations	s, if necessary:							
11.	Nor	n-establishment of	opinion with regard to novelty, inventive step and industrial applicability							
The or t	e qu o be	estions whether the industrially applica	e claimed invention appears to be novel, to involve an inventive step (to be non-obvious), able have not been and will not be examined in respect of:							
		the entire internation	onal application,							
	×	claims Nos. 1-6 pa	rtially,							
oec	aus	e:								
		the said internation not require an inter	nal application, or the said claims Nos. relate to the following subject matter which does mational preliminary examination (specify):							





WRITTEN OPINION

International application No. PCT/JP99/03929

	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
×	no international search report has been established for the said claims Nos. 1-6 partially.

- V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- 1. Statement

Novelty (N)

Claims

Inventive step (IS)

Claims 1-6

Industrial applicability (IA)

Claims

2. Citations and explanations

see separate sheet



WRITTEN OPINION SEPARATE SHEET

International application No. PCT/JP99/03929

- 1. The search authority raised an objection for lack of unity of the application. Since no required additional search fees were paid by the applicant, search has only been carried out on the invention first mentioned in the claims i.e. Seq. ID Nos 1,11 and 21. Examination can thus only be based on said subject-matter.
- 2. The present application relates to a protein having the amino acid sequence shown in Seq ID No 1, the cDNA shown in Seq. ID Nos 11 and 21, expression vectors comprising these sequences and transformed eucaryotic hosts.

 The DNA sequences have been selected from cDNA libraries by the presence of a hydrophobic region being a putative secretory signal or transmembrane.

 In particular the clone HP01550 (Seq. ID Nos 1,11,and 21) is a clone from a human stomach cancer cDNA library which consists of 65-bp 5'-untranslated region, a 378-bp ORF, and a 67-bp 3' untranslated region. The ORF codes for a protein of 125 amino acids and the expressed protein has a molecular weight of 15 kDa. Search in a protein data base revealed a similarity to the Caenorhabditis elegans hypothetical proteins F45G2.c and F45G2.c. In addition the search of the GenBank revealed an EST which shares more than 90% homology.
- 3. As far as patentability of the specific claimed sequences are concerned the following considerations apply:

The specific claimed sequences are new according to the requirements set out in Article 33(2) PCT.

However, an inventive step cannot be recognized because in general the provision of a DNA sequence without an indication of how to use said DNA sequence (specific technical purpose) is not inventive per se (Article 33(3) PCT). This also apply to the encoded protein even if expression has been carried out.

It should be noted, that all subject-matter which might involve a certain contribution to the art, namely the determination of the function of the protein and methods which make use of said protein and the encoding DNA sequence have not been carried out. Therefore an inventive step is not recognized by the present authority for claims 1-6 (Article 33(3) PCT.

PCT

NOTIFICATION OF RECEIPT OF **RECORD COPY**

(PCT Rule 24.2(a))



From the INTERNATIONAL BUREAU

To:

AOYAMA, Tamotsu **AOYAMA & PARTNERS** IMP Building 3-7, Shiromi 1-chome, Chuo-ku Osaka-shi Osaka 540-0001 **JAPON**

Date of mailing (day/month/year) 17 August 1999 (17.08.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 661102	International application No. PCT/JP99/03929

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SAGAMI CHEMICAL RESEARCH CENTER et al (for all designated States except US) KATO, Seishi et al (for US)

International filing date

22 July 1999 (22.07.99) 24 July 1998 (24.07.98)

Priority date(s) claimed

07 August 1998 (07.08.98) 25 August 1998 (25.08.98) 09 September 1998 (09.09.98) 29 September 1998 (29.09.98)

Date of receipt of the record copy by the International Bureau

06 August 1999 (06.08.99)

List of designated Offices

AP :GH,GM,KE,LS,MW,SD,SZ,UG,ZW

EA:AM,AZ,BY,KG,KZ,MD,RU,TJ,TM EP:AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE

OA:BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG

National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CU,CZ,DE,DK,EE,ES,FI,GB,GD,GE, $\mathsf{GH}, \mathsf{GM}, \mathsf{HR}, \mathsf{HU}, \mathsf{ID}, \mathsf{IL}, \mathsf{IN}, \mathsf{IS}, \mathsf{JP}, \mathsf{KE}, \mathsf{KG}, \mathsf{KR}, \mathsf{KZ}, \mathsf{LC}, \mathsf{LK}, \mathsf{LR}, \mathsf{LS}, \mathsf{LT}, \mathsf{LU}, \mathsf{LV}, \mathsf{MD}, \mathsf{MG}, \mathsf{MK}, \mathsf{MN}, \mathsf{MW}, \mathsf{MX}, \mathsf{NO}, \mathsf{MG}, \mathsf{MK}, \mathsf{MN}, \mathsf{MK}, \mathsf{MK},$

NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,US,UZ,VN,YU,ZA,ZW

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer:

M. Sakai

Telephone No. (41-22) 338.83.38

Facsimile No. (41-22) 740.14.35

Form PCT/IB/301 (July 1998)

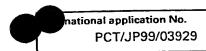
002792677



NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 17 August 1999 (17.08.99)	IMPORTANT NOTIFICATION				
Applicant's or agent's file reference	International application No.				
661102	PCT/JP99/03929				
ATTENTION The applicant should carefully check the data application of applications applications.	ppearing in this Notification. In case of any discrepancy between these data on, the applicant should immediately inform the International Bureau.				
and the indications in the international application in addition, the applicant's attention is drawn to	the information contained in the Annex, relating to:				
X time limits for entry into the national phase					
X confirmation of precautionary designation					
requirements regarding priority documer					
	ing Office and to the International Searching Authority.				
	_				





INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is 20 MONTHS from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, 30 MONTHS from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn before the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice by the applicant. There will be no reminder and no invitation. Confirmation of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.





From the INTERNATIONAL BUREAU

To:

AOYAMA, Tamotsu **AOYAMA & PARTNERS** IMP Building 3-7, Shiromi 1-chome, Chuo-ku Osaka-shi Osaka 540-0001 **JAPON**

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 06 October 1999 (06.10.99)	
Applicant's or agent's file reference 661102	IMPORTANT NOTIFICATION
International application No. PCT/JP99/03929	International filing date (day/month/year) 22 July 1999 (22.07.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 July 1998 (24.07.98)

SAGAMI CHEMICAL RESEARCH CENTER et al

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office or PCT receiving Office

Date of receipt of priority document

24 July 1998 (24.07.98)

10/208820

JP

27 Sept 1999 (27.09.99)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Juan Cruz

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

AOYAMA, Tamotsu Aoyama & Partners IMP Building 3-7, Shiromi 1-chome, Chuo-ku Osaka-shi Osaka 540-0001 JAPON



Date of mailing (day/month/year)

03 February 2000 (03.02.00)

Applicant's or agent's file reference

International application No.

PCT/JP99/03929

661102

International filing date (day/month/year)

22 July 1999 (22.07.99)

Priority date (day/month/year)
24 July 1998 (24.07.98)

IMPORTANT NOTICE

Applicant

SAGAMI CHEMICAL RESEARCH CENTER et al

 Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice: AU,CN,EP,IL,JP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,

SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

 Enclosed with this Notice is a copy of the international application as published by the International Bureau on 03 February 2000 (03.02.00) under No. WO 00/05367

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

J. Zahra

Telephone No. (41-22) 338.83.38



From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)



AOYAMA, Tamotsu Aoyama & Partners **IMP** Building 3-7, Shiromi 1-chome, Chuo-ku Osaka-shi Osaka 540-0001 JAPON

Date of mailing (day/month/year) 01 March 2000 (01.03.00)

Applicant's or agent's file reference 661102

International filing date (day/month/year)

22 July 1999 (22.07.99)

Priority date (day/month/year) 24 July 1998 (24.07.98)

IMPORTANT INFORMATION

International application No. PCT/JP99/03929

Applicant

SAGAMI CHEMICAL RESEARCH CENTER et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP :GH,GM,KE,LS,MW,SD,SL,SZ,UG,ZW

EP:AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE

National: AU, BG, BR, CA, CN, CZ, DE, IL, JP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA:AM,AZ,BY,KG,KZ,MD,RU,TJ,TM

OA:BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG

National :AE,AL,AM,AT,AZ,BA,BB,BY,CH,CU,DK,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,

ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MW,MX,PT,SD,SG,SI,SL,TJ,

TM.TR.TT.UA.UG,UZ,VN,YU,ZA,ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer:

R. Forax

Telephone No. (41-22) 338.83.38

The International Bureau of WIPO

From the NTERNATIONAL PRELIMINARY EXAM	MINING AUTHORITY	,	PCT
To: AOYAMA, Tamotsu et al. Aoyama & Partners IMP Building, 3-7, Shirom 1-chome, Chuo-ku, Osaka-s Osaka 540-0001 JAPON	hi 受付 12.2.25	OF DEMAND PRELIMIN	CIFICATION OF RECEIPT BY COMPETENT INTERNATIONAL ARY EXAMINING AUTHORITY tales 59.3(e) and 61.1(b), first sentence nistrative Instructions, Section 601(a))
		Date of mailing (day month year)	1 8. 02. 00
Applicant's or agent's file reference 661102		ІМРО	RTANT NOTIFICATION
International application No.	International filing date 22/07/1999		Priority date (day month year) 24/07/1998
PCT/ JP 99/ 03929	22/07/1999		
Applicant SAGAMI CHEMICAL RESEAR	CH CENTER et a	1.	
The applicant is hereby notified that date of receipt of the demand for integrated that demand for integrated that demand for integrated that demand for integrated that demand for integrated the demand for integrated that demand for integrated the demand for integrated t	ernational preliminary ex	inary Examining Authoramination of the intern	ority considers the following date as the national application:
(Form PCT/IPEA/404), 3. ATTENTION: That date of reelection(s) made in the demand	of the demand on behalf uthority has, in response received the required cor eccipt is AFTER the expi d does (do) not have the	to the invitation to corrections. ration of 19 months freeffect of postponing the Market 20(1). There	om the priority date. Consequently, the e entry into the national phase until 30 fore, the acts for entry into the national
months from the priority date phase must be performed with the PCT Applicant's Guide, Vo	(or later in some Offices in 20 months from the plume II.	oriority date (or later in	some Offices) (Article 22). For details, see

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465

Authorized officer

DANISSEN P T

Tel. (+49-89) 2399-8862





PCT

REC'D 15 NOV 2000
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's o	r ager	nt's file reference	FOR FURTHER ACTION		cation of Transmittal of International
661102 FOR FURTHER			FOR FURTHER ACTION	Preliminar	y Examination Report (Form PCT/IPEA/416)
nternational	applic	ation No.	International filing date (day/mont	h/year)	Priority date (day/month/year)
CT/JP99	/039	29	22/07/1999		24/07/1998
C12N15/1		nt Classification (IPC) or r	national classification and IPC		
Applicant SAGAMI (CHE	MICAL RESEARCH	CENTER et al.		
1. This in and is	terna trans	tional preliminary examitted to the applicant	mination report has been prepare according to Article 36.	d by this Int	ernational Preliminary Examining Authority
2. This R	EPO	RT consists of a total of	of 5 sheets, including this cover	sheet.	
be (s	en a ee Ri	mended and are the b	asis for this report and/or sheets 607 of the Administrative Instruct	containing r	on, claims and/or drawings which have rectifications made before this Authority the PCT).
3. This re	eport		elating to the following items:		
1	×	Basis of the report			
П	L⊒ 1521	Priority	f opinion with regard to novelty, in	wontivo eta	n and industrial applicability
111	⊠ □			ivelilive ste	p and industrial applicability
۱۷ ۷		Lack of unity of inver Reasoned statement citations and explana		novelty, in	ventive step or industrial applicability;
VI		Certain documents			
VII		Certain defects in the	e international application		
VIII		Certain observations	on the international application		
Date of sub	missio	on of the demand	Date o	of completion	of this report
03/02/20	00		13.11.	2000	
Name and preliminary	exam	g address of the internation	onal Autho	rized officer	Second State
<u></u>	D-8	opean Patent Office 0298 Munich +49 89 2399 - 0 Tx: 523	Volib	ach, S	(AM TO MARKED)
		: +49 89 2399 - 4465		hone No +49	89 2399 8715



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/JP99/03929

1.	Basis	of ti	ne report
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		•								
	This report has been drawn on the basis of (substitute sheets which have been fumished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).): Description, pages:									
	1-12	1	as originally filed							
	Clair	ns, No.:								
	1-6		as originally filed							
	Drav	vings, sheets:								
	1/50	-50/50	as originally filed							
2.	With lang	regard to the lan uage in which the	guage, all the elements marked above were available or fumished to this Authority in the international application was filed, unless otherwise indicated under this item.							
	The	se elements were	available or furnished to this Authority in the following language: , which is:							
		the language of a	translation furnished for the purposes of the international search (under Rule 23.1(b)).							
		the language of p	oublication of the international application (under Rule 48.3(b)).							
		the language of a 55.2 and/or 55.3)	translation furnished for the purposes of international preliminary examination (under Rule							
3.	With inte	n regard to any nu rnational prelimina	icleotide and/or amino acid sequence disclosed in the international application, the arry examination was carried out on the basis of the sequence listing:							
		contained in the	international application in written form.							
		filed together with	h the international application in computer readable form.							
		fumished subsec	quently to this Authority in written form.							
		furnished subsec	quently to this Authority in computer readable form.							
		the international	nat the subsequently furnished written sequence listing does not go beyond the disclosure in application as filed has been furnished.							
		The statement the listing has been	nat the information recorded in computer readable form is identical to the written sequence furnished.							
4.	The	amendments ha	ve resulted in the cancellation of:							
		the description,	pages:							
		the claims,	Nos.:							



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/JP99/03929

		the drawings,	sheets:								
5.		This report has been considered to go bey	established ond the disc	as if (sor losure as	ne of) th filed (R	ie amendn Iule 70.2(c	nents had)):	not been m	ade, sin	ce they ha	ive been
		(Any replacement sh report.)	neet containir	ng such a	mendm	ents must	be referre	d to under i	item 1 ar	nd annexe	d to this
6.	Adc	litional observations, i	if necessary:								
111.	Noi	n-establishment of o	pinion with	regard to	o novelt	ty, inventi	ve step aı	nd industri	al applic	ability	
Th	e at	uestions whether the o	claimed inver	tion app	ears to b	oe novel, te	o involve a				ovious),
		the entire internation	nal application	n.							
	×	claims Nos. 1-6 part	ially.								
be	cau	se:									
		the said internationa not require an interr	al application national prelir	, or the saninary ex	aid claim aminatio	ns Nos. re on (<i>specif</i>)	late to the /):	following s	ubject m	atter which	h does
		the description, clai that no meaningful o	ms or drawin opinion could	gs (<i>indica</i> be forma	ate parti ed (spec	cular elem cify):	ents belov	w) or said c	laims No	s. are so	unclear
		the claims, or said o	claims Nos. a	are so ina	idequate	ely suppor	ted by the	description	that no	meaningfu	ıl opinion
	Ø	no international sea	arch report ha	ıs been e	stablish	ed for the	said claim	s Nos. 1-6	partially.		
2.	an	meaningful internatior d/or amino acid seque structions:	nal preliminar ence listing to	y examin o comply	ation re with the	port canno standard	ot be carrie provided f	ed out due t or in Annex	o the fail C of the	ure of the Administr	nucleotid rative
		the written form has	s not been fu	rnished c	r does r	not comply	with the s	tandard.			
		the computer reada	able form has	not beer	n furnish	ed or does	s not comp	oly with the	standard	d.	
٧	'. Re	easoned statement ι tations and explanat	ınder Article tions suppor	35(2) wi	th rega h stater	rd to nove ment	elty, inven	ntive step o	or indust	trial applic	cability;
1	. St	atement									
	Nic	ovelty (N)	Yes:	Claims	1-6						







International application No. PCT/JP99/03929

No:

Claims

Inventive step (IS)

Yes:

Claims

No:

Claims 1-6

Industrial applicability (IA)

Yes: Claims

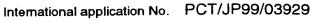
No:

Claims 1-6

2. Citations and explanations see separate sheet







EXAMINATION REPORT - SEPARATE SHEET

- The search authority raised an objection for lack of unity of the application. Since no required additional search fees were paid by the applicant, search has only been carried out on the invention first mentioned in the claims i.e. Seq. ID Nos 1,11 and 21. Examination can thus only be based on said subject-matter.
- The present application relates to a protein having the amino acid sequence 2. shown in Seq ID No 1, the cDNA shown in Seq. ID Nos 11 and 21, expression vectors comprising these sequences and transformed eucaryotic hosts. The DNA sequences have been selected from cDNA libraries by the presence of a hydrophobic region being a putative secretory signal or transmembrane. In particular the clone HP01550 (Seq. ID Nos 1,11,and 21) is a clone from a human stomach cancer cDNA library which consists of 65-bp 5'-untranslated region, a 378-bp ORF, and a 67-bp 3' untranslated region. The ORF codes for a protein of 125 amino acids and the expressed protein has a molecular weight of 15 kDa. Search in a protein data base revealed a similarity to the Caenorhabditis elegans hypothetical proteins F45G2.c and F45G2.c. In addition the search of the GenBank revealed an EST which shares more than 90% homology.
- As far as patentability of the specific claimed sequences are concerned the 3. following considerations apply:

The specific claimed sequences are new according to the requirements set out in Article 33(2) PCT.

However, an inventive step cannot be recognized because in general the provision of a DNA sequence without an indication of how to use said DNA sequence (specific technical purpose) is not inventive per se (Article 33(3) PCT) and cannot be regarded as industrial applicable. This also apply to the encoded protein even if expression has been carried out.

It should be noted, that any subject-matter which might involve a certain contribution to the art, namely the determination of the function of the protein and methods which make use of said protein and the encoding DNA sequence have not been carried out. Therefore an inventive step is not recognized by the present authority for claims 1-6 (Article 33(3) PCT).

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

AOYAMA, Tamotsu et al. Aoyama & Partners IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi Osaka 540-0001 JAPON



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)

Date of mailing (day/month/year)

13.11.2000

24/07/1998

Applicant's or agent's file reference 661102

International filing date (day/month/year)

Priority date (day/month/year)

IMPORTANT NOTIFICATION

International application No. PCT/JP99/03929

International filing date (day/mon 22/07/1999

Applicant

SAGAMI CHEMICAL RESEARCH CENTER et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich

Tel. +49 89 2399 - 0 Tx: 523656 epmu d

Fax: +49 89 2399 - 4465

Authorized officer

Emslander, S

Tel.+49 89 2399-8718





PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

61102	agent's file reference	FOR FURTHER ACTION P	ee Notification of Transmittal of International reliminary Examination Report (Form PCT/IPEA/416)
661102		POR FORTILE ACTION F	
International application No. Internation		International filing date (day/month/yea	i
CT/JP99	/03929	22/07/1999	24/07/1998
nternational 212N15/1		c) or national classification and IPC	
pplicant			
SAGAMI (CHEMICAL RESEAF	RCH CENTER et al.	
1. This in and is	ternational preliminary transmitted to the app	examination report has been prepared by licant according to Article 36.	this International Preliminary Examining Authority
2. This R	EPORT consists of a t	total of 5 sheets, including this cover shee	et.
he	en amended and are	npanied by ANNEXES, i.e. sheets of the c the basis for this report and/or sheets con ction 607 of the Administrative Instructions	description, claims and/or drawings which have taining rectifications made before this Authority sunder the PCT).
Those	annexes consist of a	total of sheets.	
Hese	armexes consist of a	total of Shoster	
3. This r	_	ons relating to the following items:	
1	☐ Basis of the rep		
1 11	☐ Basis of the rep☐ Priority	ort	ntive step and industrial applicability
1 11 111	☒ Basis of the rep☐ Priority☒ Non-establishm	ort ent of opinion with regard to novelty, inver	ntive step and industrial applicability
1 11	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state 	ort ent of opinion with regard to novelty, inver invention ement under Article 35(2) with regard to no	ntive step and industrial applicability ovelty, inventive step or industrial applicability;
 V 	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state 	ort ent of opinion with regard to novelty, inver invention ement under Article 35(2) with regard to no epilanations suporting such statement	
 V	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state citations and ex ☐ Certain docum 	ort ent of opinion with regard to novelty, inver invention ement under Article 35(2) with regard to no coplanations suporting such statement ents cited	
 	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state citations and ex ☐ Certain docum ☐ Certain defects 	ort ent of opinion with regard to novelty, inver invention ement under Article 35(2) with regard to no epilanations suporting such statement	
 V 	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state citations and ex ☐ Certain docum ☐ Certain defects 	ent of opinion with regard to novelty, inversivention ement under Article 35(2) with regard to not explanations suporting such statement ents cited in the international application ations on the international application	ovelty, inventive step or industrial applicability;
 V 	 ☒ Basis of the rep ☐ Priority ☒ Non-establishm ☐ Lack of unity of ☒ Reasoned state citations and ex ☐ Certain docum ☐ Certain defects 	ent of opinion with regard to novelty, inversivention ement under Article 35(2) with regard to not explanations suporting such statement ents cited in the international application ations on the international application	
 V 	Basis of the rep Priority Non-establishm Lack of unity of Reasoned state citations and ex Certain docum Certain defects Certain observa	ent of opinion with regard to novelty, inversivention ement under Article 35(2) with regard to not explanations suporting such statement ents cited in the international application ations on the international application	ovelty, inventive step or industrial applicability;
	Basis of the rep Priority Non-establishm Lack of unity of Reasoned state citations and ex Certain docum Certain defects Certain observa	ent of opinion with regard to novelty, inversion ement under Article 35(2) with regard to not explanations suporting such statement ents cited in the international application ations on the international application Date of contents of the international application at the international application in the internation in the international application in the international application in the internation in the inter	ovelty, inventive step or industrial applicability; completion of this report
	Basis of the rep Priority Non-establishm Lack of unity of Reasoned state citations and ex Certain docum Certain defects Certain observa	ent of opinion with regard to novelty, inversion ement under Article 35(2) with regard to not explanations suporting such statement ents cited in the international application ations on the international application Date of content of the international application of the international application of the international application of the international application of the international o	ovelty, inventive step or industrial applicability; completion of this report do officer



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP99/03929

I. Basis of the report						
1.	resp the r	onse to an invitation	irawn on the basis of (substitute sheets which have been fumished to the receiving Office i on under Article 14 are referred to in this report as "originally filed" and are not annexed to to not contain amendments (Rules 70.16 and 70.17).):			
	1-12	·	as originally filed			
	Clai	ms, No.:				
	1-6		as originally filed			
	Dra	wings, sheets:				
	1/50)-50/50	as originally filed			
2.	With lang	n regard to the lan guage in which the	guage, all the elements marked above were available or furnished to this Authority in the international application was filed, unless otherwise indicated under this item.			
	The	se elements were	available or furnished to this Authority in the following language: , which is:			
		the language of a	a translation furnished for the purposes of the international search (under Rule 23.1(b)).			
			oublication of the international application (under Rule 48.3(b)).			
		the language of a 55.2 and/or 55.3)	a translation furnished for the purposes of international preliminary examination (under Rule).			
3	. Wit inte	h regard to any n u ernational prelimina	icleotide and/or amino acid sequence disclosed in the international application, the ary examination was carried out on the basis of the sequence listing:			
		contained in the	international application in written form.			
		filed together wit	h the international application in computer readable form.			
		fumished subsec	quently to this Authority in written form.			
		and the state of the second transfer and the state of the second				
		The statement the the international	nat the subsequently furnished written sequence listing does not go beyond the disclosure i application as filed has been furnished.			
		The statement the listing has been	nat the information recorded in computer readable form is identical to the written sequence furnished.			
4	4. Th	e amendments ha	ve resulted in the cancellation of:			
		the description,	pages:			
	П	the claims.	Nos.:			



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/JP99/03929

		the drawings,	sheets:
5.			established as if (some of) the amendments had not been made, since they have been ond the disclosure as filed (Rule 70.2(c)):
		(Any replacement sh report.)	eet containing such amendments must be referred to under item 1 and annexed to this
6.	Add	litional observations, i	necessary:
111.	noN	n-establishment of o	oinion with regard to novelty, inventive step and industrial applicability
			aimed invention appears to be novel, to involve an inventive step (to be non-obvious), e have not been examined in respect of: al application.
	×	claims Nos. 1-6 part	ally.
be	caus	se:	
			application, or the said claims Nos. relate to the following subject matter which does ational preliminary examination (<i>specify</i>):
			ns or drawings (indicate particular elements below) or said claims Nos. are so unclear pinion could be formed (specify):
		the claims, or said c could be formed.	aims Nos. are so inadequately supported by the description that no meaningful opinion
	×	no international sea	ch report has been established for the said claims Nos. 1-6 partially.
2.	and	neaningful internation d/or amino acid seque tructions:	al preliminary examination report cannot be carried out due to the failure of the nucleotide ace listing to comply with the standard provided for in Annex C of the Administrative
		the written form has	not been furnished or does not comply with the standard.
		the computer reada	ole form has not been furnished or does not comply with the standard.
V			nder Article 35(2) with regard to novelty, inventive step or industrial applicability; ons supporting such statement
1	. Sta	atement	
	No	velty (N)	Yes: Claims 1-6







International application No. PCT/JP99/03929

No:

Claims

Inventive step (IS)

Yes:

Claims

No:

Claims 1-6

Industrial applicability (IA)

Yes:

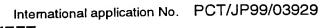
Claims

No:

Claims 1-6

2. Citations and explanations see separate sheet





INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

- The search authority raised an objection for lack of unity of the application. Since no required additional search fees were paid by the applicant, search has only been carried out on the invention first mentioned in the claims i.e. Seq. ID Nos 1,11 and 21. Examination can thus only be based on said subject-matter.
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661102





PCT REQUEST

Original (for SUBMISSION) - printed on 16.07.1999 10:35:27 AM

1/5

	·	
0	For receiving Office use only	
0-1	International Application No.	PCT
0-2	International Filing Date	22.7.99
0-3	Name of receiving Office and "PCT International Application"	文領印
0-4	Form - PCT/RO/101 PCT Request	1
0-4-1	Prepared using	PCT-EASY Version 2.84 (updated 01.07.1999)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Japanese Patent Office (RO/JP)
0-7	Applicant's or agent's file reference	661102
1	Title of invention	HUMAN PROTEINS HAVING HYDROPHOBIC DOMAINS AND DNAs ENCODING THESE PROTEINS
īi	Applicant	
II-1	This person is:	applicant only
11-2	Applicant for	all designated States except US
II- 4	Name	SAGAMI CHEMICAL RESEARCH CENTER
11-5	Address:	4-1, Nishi-Ohnuma 4-chome,
		Sagamihara-shi, Kanagawa 229-0012 Japan
II-6	State of nationality	JP
11-7	State of residence	JP
111-1	Applicant and/or inventor	
111-1-1	This person is:	applicant only
III-1-2	Applicant for	all designated States except US
111-1-4	Name	PROTEGENE INC.
III-1-5	Address:	2-20-3, Naka-cho,
		Meguro-ku, Tokyo 153-0065
		Tanan
		Juapan
III-1-6	State of nationality	Japan JP





PCT REQUEST

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2/5

111-2	Applicant and/or inventor	
111-2-1	This person is:	applicant and inventor
111-2-2	Applicant for	US only
111-2-4	Name (LAST, First)	KATO, Seishi
111-2-5	Address:	3-46-50, Wakamatsu,
		Sagamihara-shi, Kanagawa 229-0014
-	·	Japan
111-2-6	State of nationality	JP
III-2-7	State of residence	JP
111-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
111-3-2	Applicant for	US only
111-3-4	Name (LAST, First)	KIMURA, Tomoko
111-3-5	Address:	302, 4-1-28, Nishiikuta, Tama-ku,
		Kawasaki-shi, Kanagawa 214-0037
		Japan
111-3-6	State of nationality	JP
111-3-7	State of residence	JP
IV-1	Agent or common representative; or	
	address for correspondence The person identified below is hereby/has	
	been appointed to act on behalf of the	agent
	applicant(s) before the competent	
IV-1-1	International Authorities as: Name (LAST, First)	AOYAMA, Tamotsu
	Address:	AOYAMA & PARTNERS
IV-1-2	Address.	IMP Building, 3-7, Shiromi 1-chome,
		chuo-ku,
		Osaka-shi, Osaka 540-0001
		·
	1	Japan (06) 6040, 1361
IV-1-3	Telephone No.	(06) 6949-1261
IV-1-4	Facsimile No.	(06) 6949-0361
IV-2	Additional agent(s)	additional agent(s) with same address as
		first named agent
IV-2-1	Name(s)	TAMURA, Yasuo; IWASAKI, Mitsutaka

661102



PCT REQUEST

Original (for SUBMISSION) - printed on 16.07.1999 10:35:27 AM

3/5

v	Designation of States	
V-1	Regional Patent	AP: GH GM KE LS MW SD SZ UG ZW and any
	(other kinds of protection or treatment, if any, are specified between parentheses	other State which is a Contracting State
	after the designation(s) concerned)	of the Harare Protocol and of the PCT
		EA: AM AZ BY KG KZ MD RU TJ TM and any
	1	other State which is a Contracting State
		of the Eurasian Patent Convention and of
	1 .	the PCT
		EP: AT BE CH&LI CY DE DK ES FI FR GB GR
		IE IT LU MC NL PT SE and any other State
		which is a Contracting State of the
		European Patent Convention and of the
		PCT
		OA: BF BJ CF CG CI CM GA GN GW ML MR NE
		SN TD TG and any other State which is a
		member State of OAPI and a Contracting
		State of the PCT
V-2	National Patent (other kinds of protection or treatment, if	AE AL AM AT AU AZ BA BB BG BR BY CA
	any are specified between parentheses	CHELI CN CU CZ DE DK EE ES FI GB GD GE
	after the designation(s) concerned)	GH GM HR HU ID IL IN IS JP KE KG KR KZ
		LC LK LR LS LT LU LV MD MG MK MN MW MX
		NO NZ PL PT RO RU SD SE SG SI SK SL TJ
		TM TR TT UA UG US UZ VN YU ZA ZW
V-5	Precautionary Designation Statement	
	In addition to the designations made under items V-1, V-2 and V-3, the applicant also	
	makes under Rule 4.9(b) all designations	
	which would be permitted under the PCT	
	except any designation(s) of the State(s) indicated under item V-6 below. The	
	applicant declares that those additional	
	designations are subject to confirmation and that any designation which is not	
	confirmed before the expiration of 15	
	months from the priority date is to be	
	regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	24 July 1998 (24.07.1998)
VI-1-2	Number	Patent Application No. 10-208820
VI-1-3		JP
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	07 August 1998 (07.08.1998)
VI-2-2	Number	Patent Application No. 10-224105
VI-2-3	Country	JP



PCT REQUEST

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1-3	Priority claim of earlier national application		,		
1-3-1	Filing date	25 August 1998 (25.08			
1-3-2	Number	Patent Application No. 10-238116			
/1-3-3	Country	JP			
/1-4	Priority claim of earlier national				
/I-4-1	application Filing date	09 September 1998 (09	0.09.1998)		
√I-4-2	Number	Patent Application No			
√I-4-3	Country	J₽			
VI-5	Priority claim of earlier national				
	application	29 September 1998 (29	0.00.10081		
VI-5-1	Filing date				
VI-5-2	Number	Patent Application No	5. 10-275505		
VI-5-3	Country	JP	(EDO) (IG) (ED)		
VII-1	International Searching Authority Chosen	European Patent Offic	ce (EPO) (ISA/EP)		
VIII	Check list	number of sheets	electronic file(s) attached		
VIII-1	Request	5			
VIII-2	Description (excluding sequence listing part)	121	-		
VIII-3	Claims	1	_		
VIII-4	Abstract	1	661102.txt		
VIII-5	Drawings	50	_		
VIII-6	Sequence listing part of description	177	_		
VIII-7	TOTAL	355			
	Accompanying items	paper document(s) attached	electronic file(s) attached		
VIII-8	Fee calculation sheet	✓	<u> </u>		
VIII-9	Separate signed power of attorney	✓			
VIII-15	Nucleotide and/or amino acid sequence listing in computer readable form		separate diskette		
VIII-16	PCT-EASY diskette	-	diskette		
VIII-17	Other (specified):	Revenue stamps of			
		transmittal fee for			
		receiving office			
VIII-17	Other (specified):	Certificate of	-		
		payment of basic &			
		designation fee for			
		International Bureau			
VIII-17	Other (specified):	Certificate of	-		
		payment of search	_		
		fee for EPO			
VIII-18	Figure of the drawings which should accompany the abstract				
VIII-19	Language of filing of the international	English			
IX-1	application Signature of applicant or agent	1677			
	,	1 / Men			





5/5

PCT REQUEST

Original (for SUBMISSION) - printed on 16.07.1999 10:35:27 AM

661102

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by		
	the International Bureau	 	





1/2

PCT (ANNEX - FEE CALCULATION SHEET) Original (for SUBMISSION) - printed on 16.07.1999 10:35:27 AM

661102

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only		
0-1	International Application No.		
0-2	Date stamp of the receiving Office		
)-4	Form - PCT/RO/101 (Annex)	T	
)- 4 -1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Vers	ion 2.84
J-4-1	Tepared doming	(updated 01.0	
0-9	Applicant's or agent's file reference	661102	,
2	Applicant	<u> </u>	AL RESEARCH CENTER, et al.
<u>-</u> 12	Calculation of prescribed fees	fee amount/multiplier	total amounts (JPY)
12-1	Transmittal fee	「 ⇔	18,000
12-2	Search fee	\$ ⇒	120,000
12-3	International fee		
•	Basic fee		
	(first 30 sheets) b	1	
12-4	Remaining sheets	325	
12-5	Additional amount (X	1,300	
12-6	Total additional amount b	422,500	
12-7	b1 + b2 =	477,300	
12-8	Designation fees Number of designations contained ir international application	78	
12-9	Number of designation fees payable (maximum 10)	10	
12-10	Amount of designation fee (X	12,600	
12-11	Total designation fees	126,000	
12-12	PCT-EASY fee reduction	-16,900	
12-13	Total International fee (B+D-R)	⇒	586,400
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇨	724,400
12-19	Mode of payment	Transmittal f	ee: revenue stamps
		Search fee: b	
			fee: bank draft
			ment fee: revenue stamps
	VAL	IDATION LOG AND R	EMARKS
13-1-1	Applicant remarks		ttorney AOYAMA Tamotsu
	Names		ttorney TAMURA Yasuo
		6703 Patent A	ttorney IWASAKI Mitsutaka
13-2-1	Validation messages	Green?	
	Request	1	the invention should
		_	entered in capital
		letters. Plea	se verify.



From the INTERNATIONAL SEARCHING AUTHORITY To: NOTIFICATION OF RECEIPT Aoyama & Partners OF SEARCH COPY 8,23 Attn. AOYAMA, T IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi (PCT Rule 25.1) Osaka 540-0001 **JAPAN** Date of mailing (day/month/year) 20/08/1999 Applicant's or agent's file reference IMPORTANT NOTIFICATION 661102 International filing date(day/month/year) Priority date (day/month/year) International application No. PCT/JP 99/03929 22/07/1999 24/07/1998 Applicant SAGAMI CHEMICAL RESEARCH CENTER et al. Where the International Searching Authority and the Receiving Office are not the same office: The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below. Where the International Searching Authority and the Receiving Office are the same office: The applicant is hereby notified that the search copy of the international application was received on the date indicated below. 05/08/1999 __ (date of reæipt). The search copy was accompanied by a nuclectide and/or amino acid sequence listing in computer readable form. 2. 3. Time limit for establishment of International Search Report The applicant is informed that the time limit for establishing the International Search Report is 3 months from the date of receipt indicated above or 9 morths from the priority date, whichever time limit expires later A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, 4. to the Receiving Office. Name and mailing address of the International Searching Authority Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 ISA/EP NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016

TENT COOPERATION T

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

- .

Assistant Commissioner for Patents United States Patent and Trademark Office

Office Box PCT

661102

Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE

nternational application No.	Applicant's or agent's file reference
C1 March 2000 (01.03.00)	in its capacity as elected Office
Date of mailing (day/month/year)	[]

International filing date (day/month/year)
22 July 1999 (22.07.99)

Priority date (day/month/year) 24 July 1998 (24.07.98)

Applicant

KATO, Seishi et al

PCT/JP99/03929

er
e

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

R. Forax

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL SEARCHING AUTHORITY To NOTIFICATION OF TRANSMITTAL OF Aoyama & Partners HE INTERNATIONAL SEARCH REPORT Attn. AOYAMA, T IMP Building, 3-7, Shiromi OR THE DECLARATION 12.3.27 1-chome, Chuo-ku, Osaka-shi (PCT Rule 44.1) Osaka 540-0001 JAPAN Date of mailing (day/month/year) 06/03/2000 Applicant's or agent's file reference FOR FURTHER ACTION See paragraphs 1 and 4 below 661102 International filing date International application No. (day/month/year) 22/07/1999 PCT/JP 99/03929 Applicant SAGAMI CHEMICAL RESEARCH CENTER et al. The applicant is hereby notified that the International Search Report has been established and is transmitted herewith. 1. X Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46): When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet. International Bureau of WIPO Where? Directly to the 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41-22) 740.14.35 For more detailed instructions, see the notes on the accompanying sheet. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith. 3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that: the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices. no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made. 4. Further action(s): The applicant is reminded of the following: Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication. Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

priority date or could not be elected because they are not bound by Chapter II.

Authorized officer

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the

Mireille Claudepierre

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the International application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 *Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;
 claims 30, 33 and 36 unchanged; new claims 49 to 51 added.*
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide



INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
661102	ACTION	
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/JP 99/03929	22/07/1999	24/07/1998
Applicant		
SAGAMI CHEMICAL RESEARCH CENTER et al.		
This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant		
according to Article 18. A copy is being transmitted to the International Bureau.		
This International Search Report consists of a total of sheets.		
This International Search Report consists of a total of		
1. Basis of the report		
 a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item. 		
the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).		
b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search		
was carried out on the basis of the sequence listing:		
contained in the international application in written form.		
filed together with the international application in computer readable form.		
furnished subsequently to this Authority in written form.		
furnished subsequently to this Authority in computer readble form. X the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the		
international application as filed has been furnished.		
the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished		
2. Certain claims were found unsearchable (See Box I).		
3. X Unity of invention is lacking (see Box II).		
4. With regard to the title,		
the text is approved as submitted by the applicant.		
the text has been established by this Authority to read as follows:		
5. With regard to the abstract,		
5. With regard to the abstract, the text is approved as submitted by the applicant.		
the text is approved as submitted by the applicant. the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.		
i.		porty outside to this reactions.
6. The figure of the drawings to be pu	iblished with the abstract is Figure No.	None of the figures.
	plicant. ailed to suggest a figure.	
1	area to suggest a rigure. ser characterizes the invention.	
pecause tris figure bett	and the state of t	



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Claims 1-6 partially

A protein comprising amino acid sequence SEQ ID NO 1, a DNA SEQ ID NO 11 or 21, encoding this protein, as well as an expression vector capable of expressing this sequence and a eukaryotic cell expressing the DNA

2. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 2 and DNA SEQ ID 12 and 22 $\,$

3. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 3 and DNA SEQ ID 13 and 23 $\,$

4. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 4 and DNA SEQ ID 14 and 24 $\,$

5. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 5 and DNA SEQ ID 15 and 25

6. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 6 and DNA SEQ ID 16 and 36 $\,$

7. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 7 and DNA SEQ ID 17 and 37

8. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 8 and DNA SEQ ID 18 and 38 $\,$

9. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 9 and DNA SEQ ID 19 and 39



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 10 and DNA SEQ ID 20 and 30 $\,$

11. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 31 and DNA SEQ ID 41 and 51 $\,$

12. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 32 and DNA SEQ ID 42 and 52 $\,$

13. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 33 and DNA SEQ ID 43 and 53 $\,$

14. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 34 and DNA SEQ ID 44 and 54 $\,$

15. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 35 and DNA SEQ ID 45 and 55 $\,$

16. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 36 and DNA SEQ ID 46 and 56 $\,$

17. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 37 and DNA SEQ ID 47 and 57 $\,$

18. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 38 and DNA SEQ ID 48 and 58



19. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 39 and DNA SEQ ID 49 and 59 $\,$

20. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 40 and DNA SEQ ID 50 and 60 $\,$

21. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 61 and DNA SEQ ID 71 and 81 $\,$

22. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 62 and DNA SEQ ID 72 and 82 $\,$

23. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 63 and DNA SEQ ID 73 and 83 $\,$

24. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 64 and DNA SEQ ID 74 and 84 $\,$

25. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 65 and DNA SEQ ID 75 and 85 $\,$

26. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 66 and DNA SEQ ID 76 and 86

27. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 67 and DNA SEQ ID 77 and 87 $\,$

28. Claims: 1-6 partially



Idem as subject 1 but limited to protein SEQ ID NO. 68 and DNA SEQ ID 78 and 88 $\,$

29. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 69 and DNA SEQ ID 79 and 89

30. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 70 and DNA SEQ ID 80 and 90 $\,$

31. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 91 and DNA SEQ ID 101 and 111 $\,$

32. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 92 and DNA SEQ ID 102 and 112 $\,$

33. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 93 and DNA SEQ ID 103 and 113 $\,$

34. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 94 and DNA SEQ ID 104 and 114 $\,$

35. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 95 and DNA SEQ ID 105 and 115

36. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 96 and DNA SEQ ID 106 and 116 $\,$

37. Claims: 1-6 partially



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Idem as subject 1 but limited to protein SEQ ID NO. 97 and DNA SEO ID 107 and 117

38. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 98 and DNA SEQ ID 108 and 118 $\,$

39. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 99 and DNA SEQ ID 109 and 119 $\,$

40. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 100 and DNA SEQ ID 110 and 120 $\,$

41. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 121 and DNA SEQ ID 131 and 141 $\,$

42. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 122 and DNA SEQ ID 132 and 142 $\,$

43. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 123 and DNA SEQ ID 133 and 143 $\,$

44. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 124 and DNA SEQ ID 134 and 144 $\,$

45. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 125 and DNA SEQ ID 135 and 145

46. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 126 and



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

DNA SEQ ID 136 and 146

47. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 127 and DNA SEQ ID 137 and 147 $\,$

48. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 128 and DNA SEQ ID 138 and 148 $\,$

49. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 129 and DNA SEQ ID 139 and 149 $\,$

50. Claims: 1-6 partially

Idem as subject 1 but limited to protein SEQ ID NO. 130 and DNA SEQ ID 140 and 150 $\,$

INTERNATIONAL SEARCH REPORT



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705 C12N5/10 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C12N C07K IPC 7 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ^o WO 98 21328 A (KATO SEISHI ; PROTEGENE INC 1-6 Х (JP); SEKINE SHINGO (JP); SAGAMI CHEM R) 22 May 1998 (1998-05-22) abstract page 17, last paragraph -page 18, paragraph 1 DATABASE EMBLEMEST6 [Online] 1-6 X Accession Number AI057511, 22 July 1998 (1998-07-22) STRAUSBERG R: "H. sapiens cDNA clone IMAGE:1653181 3' similar to SW:YJK4 yeast P42929 hypothetical 16.2 kD protein in SME1-MEF2 intergenic region" XP002123564 100% identity in 357 BP overlap with SEQ ID NO:11 Patent family members are listed in annex. Further documents are listed in the continuation of box C. X Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *O* document referring to an oral disclosure, use, exhibition or document published prior to the international filing date but *&" document member of the same patent family later than the priority date claimed Date of mailing of the international search report Date of the actual completion of the international search **D** 6. 03. nn 23 November 1999 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, CUPIDO, M Fax: (+31-70) 340-3016

1

INTERNATIONAL SEARCH REPORT

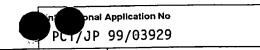


C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Relevant to claim No.
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Netevant to claim No.
X	DATABASE EMBLEST21 [Online] Accession Number AA 482452, 24 June 1997 (1997-06-24) HILLIER L ET AL.: "zv05b11.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 7527733 5'similar to SW:YJK4 yeast P42929 hypothetical 16.2 kD protein in SME1-MEF2 intergenic region" XP002123565 99.7% identity in 367 BP overlap with SEQ ID NO 11	1-6
A	D'ANDREA ET AL: "Molecular Cloning of NKB1. A Natural Killer Cell Receptor for HLA -B Allotypes" JOURNAL OF IMMUNOLOGY, vol. 155, no. 5, 1 September 1995 (1995-09-01), pages 2306-2310 2310, XP002111500 ISSN: 0022-1767 abstract page 2307, right-hand column, line 16	1-6
A	GILLEN C M ET AL: "Molecular cloning and functional expression of the K-Cl cotransporter from rabbit, rat, and human." JOURNAL OF BIOLOGICAL CHEMISTRY., vol. 271, no. 27, 5 July 1996 (1996-07-05), pages 16237-16244, XP002119528 AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD., US ISSN: 0021-9258 abstract	1-6
A	KYTE J ET AL: "A SIMPLE METHOD FOR DISPLAYING THE HYDROPATHIC CHARACTER OF A PROTEIN" JOURNAL OF MOLECULAR BIOLOGY, vol. 157, no. 1, 5 May 1982 (1982-05-05), pages 105-132, XP000609692 ISSN: 0022-2836 cited in the application the whole document	1-6
P,X	DATABASE EMBLEST11 [Online] Accession Number AI 553893, 25 March 1999 (1999-03-25) STRAUSBERG R: "Homo sapiens cDNA clone IMAGE:2169115 3'" XP002123566 100% identity in 375 BP overlap with SEQ ID 11	1-6

1

INTERNATIONAL SEARCH REPORT

ion on patent family members



Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9821328 A	22-05-1998	AU 4885297 A EP 0941320 A	03-06-1998 15-09-1999



national application No.
PCT/JP 99/03929

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of ites sneet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Int	ernational Searching Authority found multiple inventions in this international application, as follows:
se	ee additional sheets
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-6 partially
Rema	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7: C12N 15/12, C07K 14/705, C12N 5/10

A3

(11) International Publication Number:

WO 00/05367

(43) International Publication Date:

3 February 2000 (03.02.00)

(21) International Application Number:

PCT/JP99/03929

(22) International Filing Date:

22 July 1999 (22.07.99)

(30) Priority Data:

10/208820 10/224105 10/238116 10/254736 10/275505

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29 September 1998 (29.09.98)

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DESCRIPTION

Human Proteins Having Hydrophobic Domains and DNAs Encoding These Proteins

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TECHNICAL FIELD

The present invention relates to human proteins having hydrophobic domains, DNAs coding for these proteins, expression vectors for these DNAs as well as eucaryotic cells expressing these DNAs. The proteins of the present invention can be employed as pharmaceuticals or as antigens for preparing antibodies against these proteins. The human cDNAs of the present invention can be utilized as probes for the genetic diagnosis and gene sources for the gene therapy. Furthermore, the cDNAs can be utilized as gene sources for large-scale production of the proteins encoded by these into which these genes are introduced Cells express secretory proteins and membrane proteins in large amounts can be utilized for detection of the corresponding receptors and ligands, screening of novel low-molecular pharmaceuticals, and so on.

BACKGROUND ART

Cells secrete many proteins outside the cells. These important roles for the play secretory proteins proliferation control, the differentiation induction, material transportation, the biological protection, etc. in Different from intracellular proteins, cells. secretory proteins exert their actions outside the cells, whereby they can be administered in the intracorporeal manner such as the injection or the drip, so that there are

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hidden potentialities as medicines. In fact, a number of human secretory proteins such as interferons, interleukins, thrombolytic erythropoietin, agents, etc. have currently employed as medicines. In addition, secretory described proteins other than those above have undergoing clinical trials to develop as pharmaceuticals. Because it has been conceived that the human cells still produce many unknown secretory proteins, availability of these secretory proteins as well as genes coding for them is expected to lead to development of novel pharmaceuticals utilizing these proteins.

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On the other hand, membrane proteins play important roles, as signal receptors, ion channels, transporters, etc. material transportation and the transmission through the cell membrane. Examples thereof include receptors for a variety of cytokines, ion channels for the sodium ion, the potassium ion, the chloride ion, etc., transporters for saccharides and amino acids, and so on, where the genes for many of them have been cloned already. It has been clarified that abnormalities of these membrane proteins are associated with a number of hithertocryptogenic diseases. Therefore, discovery of a new membrane protein is anticipated to lead to elucidation of the causes of many diseases, so that isolation of a new gene coding for the membrane protein has been desired.

Heretofore, owing to difficulty in the purification from human cells, these secretory proteins and membrane proteins have been isolated by an approach from the gene side. A general method is the so-called expression cloning which comprises introduction of a cDNA library into eucaryotic cells to express cDNAs and then screening of the cells secreting, or expressing on the surface of membrane,

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the objective active protein. However, this method is applicable only to cloning of a gene for a protein with a known function.

In general, secretory proteins and membrane proteins possess at least one hydrophobic domain inside the proteins, after synthesis thereof in the ribosome, wherein, domain works a secretory signal or remains as in the phospholipid membrane to be trapped in the membrane. Accordingly, the evidence of this cDNA for encoding a secretory protein and a membrane protein is provided by determination of the whole base sequence of a full-length cDNA followed by detection of highly hydrophobic domain(s) in the amino acid sequence of the protein encoded by this CDNA.

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OBJECTS OF THE INVENTION

The main object of the present invention is to provide novel human proteins having hydrophobic domains, DNAs coding for these proteins, and expression vectors for these DNAs as well as transformed eucaryotic cells that are capable of expressing these DNAs. This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description with reference to the accompanying drawings.

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BRIEF DESCRIPTION OF DRAWINGS

- Fig. 1 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01550.
- Fig. 2 illustrates the hydrophobicity/hydrophilicity 30 profile of the protein encoded by clone HP02593.
 - Fig. 3 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10195.

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- Fig. 4 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10423.
- Fig. 5 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10506.
- Fig. 6 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10507.
- Fig. 7 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10548.
- Fig. 8 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10566.
- Fig. 9 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10567.
- Fig. 10 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10568.
- Fig. 11 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01426.
- Fig. 12 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02515.
- Fig. 13 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02575.
- Fig. 14 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10357.
- Fig. 15 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10447.
- Fig. 16 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10477.
 - Fig. 17 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10513.
- Fig. 18 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10540.
 - Fig. 19 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10557.

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Fig. 20 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10563.

Fig. 21 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01467.

Fig. 22 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01956.

Fig. 23 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02545.

Fig. 24 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02551.

Fig. 25 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02631.

Fig. 26 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02632.

Fig. 27 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10488.

Fig. 28 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10538.

Fig. 29 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10542.

Fig. 30 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10571.

Fig. 31 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01470.

Fig. 32 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02419.

Fig. 33 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02631.

Fig. 34 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02695.

Fig. 35 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10031.

Fig. 36 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10530.

- Fig. 37 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10541.
- Fig. 38 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10550.
 - Fig. 39 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10590.
 - Fig. 40 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10591.
 - Fig. 41 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP01462.
 - Fig. 42 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02485.
- 15 Fig. 43 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP02798.
 - Fig. 44 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10041.
 - Fig. 45 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10246.
 - Fig. 46 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10392.
 - Fig. 47 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10489.
- 25 Fig. 48 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10519.
 - Fig. 49 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10531.
- Fig. 50 illustrates the hydrophobicity/hydrophilicity profile of the protein encoded by clone HP10574.

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the result of intensive studies, the present inventors have been successful in cloning of cDNAs coding for proteins having hydrophobic domains from the human fulllength cDNA bank, thereby completing the present invention. invention provides words, the present other hydrophobic domains, namely proteins having comprising any of the amino acid sequences represented by SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. Moreover, the present invention provides DNAs coding for the above-mentioned proteins, exemplified by cDNAs comprising any of the base sequences represented by SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140, as well as expression vectors that are capable of expressing any of these DNAs by in vitro translation or in eucaryotic cells and transformed eucaryotic cells that are capable of expressing these DNAs and of producing the abovementioned proteins.

DETAILED DESCRIPTION OF THE INVENTION

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The proteins of the present invention can be obtained, for example, by a method for isolation from human organs, cell lines, etc., a method for preparation of peptides by the chemical synthesis, or a method for production with the recombinant DNA technology using the DNAs coding for the hydrophobic domains of the present invention, among which production with the recombinant method for technology is employed preferably. For instance, in vitro expression of the proteins can be achieved by preparation of an RNA by in vitro transcription from a vector having one of the cDNAs of the present invention, followed by in vitro translation using this RNA as a template. Also, introduction of the translated region into a suitable expression vector

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by the method known in the art leads to expression of a large amount of the encoded protein in prokaryotic cells such as *Escherichia coli*, *Bacillus subtilis*, etc., and eucaryotic cells such as yeasts, insect cells, mammalian cells, etc.

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In the case where one of the proteins of the present invention is produced by expressing the DNA by in vitro translation, the protein of the present invention can be produced in vitro, when the translated region of this cDNA introduced into a vector having an RNA polymerase promoter, followed by addition of the vector to an in vitro translation system such as a rabbit reticulocyte lysate or a RNA extract, containing an germ corresponding to the promoter. RNA polymerase promoters are exemplified by T7, T3, SP6, and the like. containing these RNA polymerase promoters are exemplified by pKA1, pCDM8, pT3/T7 18, pT7/3 19, pBluescript II, and so on. Furthermore, the protein of the present invention can be expressed as the secreted form or the form incorporated into the microsome membrane, when a canine pancreas microsome or the like is added to the reaction system.

In the case where one of the protein of the present expressing the DNA invention is produced by microorganism such as Escherichia coli etc., a recombinant expression vector bearing the translated region of the cDNA of the present invention is constructed in an expression vector having an origin which can be replicated in the microorganism, a promoter, a ribosome-binding site, a cDNAcloning site, a terminator etc. and, after transformation of the host cells with this expression vector, the resulting transformant is incubated, whereby the protein encoded by said cDNA can be produced on a large scale in the

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microorganism. In this case, a protein fragment containing any region can be obtained by carrying out the expression with inserting an initiation codon and a termination codon in front of and behind the selected translated region. Alternatively, a fusion protein with another protein can be expressed. Only the portion of the protein encoded by this cDNA can be obtained by cleavage of this fusion protein with a suitable protease. The expression vector for Escherichia coli is exemplified by the pUC series, pBluescript II, the pET expression system, the pGEX expression system, and so on.

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In the case where one of the proteins of the present invention is produced by expressing the DNA in eucaryotic cells, the protein of the present invention can be produced as a secretory protein or as a membrane protein on the cellmembrane surface, when the translated region of this cDNA is introduced into an expression vector for eucaryotic cells that has a promoter, a splicing region, a poly(A) addition site, etc., followed by introduction into the eucaryotic cells. The expression vector is exemplified by pKA1, pED6dpc2, pCDM8, pSVK3, pMSG, pSVL, pBK-CMV, pBK-RSV, EBV vector, pRS, pYES2, and so on. Examples of eucaryotic cells to be used in general include mammalian cultured cells such as simian kidney cells COS7, Chinese hamster ovary cells CHO, etc., budding yeasts, fission yeasts, silkworm cells, Xenopus oocytes, and so on, but any eucaryotic cells may be used, provided that they are capable of expressing the proteins of the present invention. The expression vector can be introduced into the eucaryotic cells by methods known in the art such as the electroporation method, the calcium phosphate method, the liposome method, the DEAE-dextran method, and so on.

After one of the proteins of the present invention is

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expressed in prokaryotic cells or eucaryotic cells, the objective protein can be isolated from the culture and purified by a combination of separation procedures known in the art. Such examples include treatment with a denaturing agent such as urea or a detergent, sonication, enzymatic digestion, salting-out or solvent precipitation, dialysis, centrifugation, ultrafiltration, gel filtration, SDS-PAGE, isoelectric focusing, ion-exchange chromatography, hydrophobic chromatography, affinity chromatography, reverse phase chromatography, and so on.

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The proteins of the present invention include peptide fragments (5 amino acid residues or more) containing any partial amino acid sequence in the amino acid sequences represented by SEQ ID Nos. 1. to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130. These peptide fragments can be utilized as antigens for preparation of antibodies. Hereupon, among the proteins of the present invention, those having the signal sequences are secreted in the form of mature proteins, after the signal sequences are removed. Therefore, these mature proteins shall come within the scope of the present invention. The N-terminal amino acid sequences of the mature proteins can be easily determined by using the method for the determination of cleavage site of a signal [JP 8-187100 A]. Furthermore, some proteins undergo the processing on the cell surface to be converted to the secretory forms. Such proteins or peptides in the secretory forms shall come within the scope of the present invention. In the case where sugar chain-binding sites are present in the amino acid sequences, expression in appropriate eucaryotic cells affords proteins to which sugar chains are attached. Accordingly, such proteins or peptides to which sugar chains are attached shall come within the

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scope of the present invention.

The DNAs of the present invention include all the DNAs coding for the above-mentioned proteins. These DNAs can be obtained by using a method by chemical synthesis, a method by cDNA cloning, and so on.

The cDNAs of the present invention can be cloned, for example, from cDNA libraries derived from the human cells. These cDNAs are synthesized by using as templates poly(A)* RNAs extracted from human cells. The human cells may be cells delivered from the human body, for example, by the operation or may be the cultured cells. The cDNAs can be synthesized by using any method selected from the Okayama-Berg method [Okayama, H. and Berg, P., Mol. Cell. Biol. 2: 161-170 (1982)], the Gubler-Hoffman method [Gubler, U. and Hoffman, J. Gene 25: 263-269 (1983)], and so on, but it is preferred to use the capping method [Kato, S. et al., Gene 150: 243-250 (1994)], as exemplified in Examples, in order to obtain a full-length clone in an effective manner. In addition, commercially available, human cDNA libraries can be utilized. Cloning of the cDNAs of the present invention from the cDNA libraries can be carried out by synthesis of an oligonucleotide on the basis of base sequences of any portion in the cDNA of the present invention, followed by screening using this oligonucleotide as the probe according to the colony or plaque hybridization by a method known in the art. In addition, the cDNA fragments of the present invention can be prepared by synthesis of oligonucleotides which hybridize with both termini of the objective cDNA fragment, followed by the usage of these oligonucleotides as the primers for the RT-PCR method using an mRNA isolated from human cells.

The cDNAs of the present invention are characterized by

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comprising either of the base sequences represented by SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or the base sequences represented by SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Table 1 summarizes the clone number (HP number), the cells from which the cDNA was obtained, the total base number of the cDNA, and the number of the amino acid residues of the encoded protein, for each of the cDNAs.

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Table 1

		Table 1		
				Number
SEQ ID No.	HP	Cells	Base	of amino
SEQ ID NO.	number	Cells	number	acid
				residues
1, 11, 21	HP01550	Stomach cancer	510	125
2, 12, 22	HP02593	Saos-2	697	131
3, 13, 23	HP10195	HT-1080	1619	242
4, 14, 24	HP10423	U-2 OS	1066	264
5, 15, 25	HP10506	Stomach cancer	618	112
6, 16, 26	HP10507	Stomach cancer	1021	146
7, 17, 27	HP10548	Stomach cancer	1432	344
8, 18, 28	HP10566	Stomach cancer	601	97
9, 19, 29	HP10567	Stomach cancer	585	124
10, 20, 30	HP10568	Stomach cancer	1100	327
31, 41, 51	HP01426	Stomach cancer	1065	313
32, 42, 52	HP02515	Saos-2	937	229
33, 43, 53	HP02575	Saos-2	1678	467
34, 44, 54	HP10357	Stomach cancer	467	99
35, 45, 55	HP10447	Liver	875	189
36, 46, 56	HP10477	Liver	1256	363
37, 47, 57	HP10513	Stomach cancer	884	249
38, 48, 58	HP10540	Saos-2	589	98
39, 49, 59	HP10557	Stomach cancer	673	172
40, 50, 60	HP10563	Saos-2	1425	120
61, 71, 81	HP01467	HT-1080	1436	307
62, 72, 82	HP01956	Liver	997	183
63, 73, 83	HP02545	Saos-2	1753	327
64, 74, 84	HP02551	Saos-2	1117	223
65, 75, 85	HP02631	Saos-2	1380	48
66, 76, 86	HP02632	HT-1080	1503	371
67, 77, 87	HP10488	Liver	733	90
68, 78, 88	HP10538	Saos-2	3768	499
69, 79, 89	HP10542	Stomach cancer	770	106
70, 80, 90	HP10571	Stomach cancer	1229	152

91, 101, 111	HP01470	Stomach cancer	1619	358
92, 102, 112	HP02419	Stomach cancer	2054	226
93, 103, 113	HP02631	Saos-2	1380	195
94, 104, 114	HP02695	Stomach cancer	1292	339
95, 105, 115	HP10031	Saos-2	2168	487
96, 106, 116	HP10530	Saos-2	1357	393
97, 107, 117	HP10541	Stomach cancer	711	196
98, 108, 118	HP10550	Stomach cancer	651	107
99, 109, 119	HP10590	HT-1080	1310	350
100, 110, 120	HP10591	HT-1080	1400	107
121, 131, 141	HP01462	HT-1080	2050	483
122, 132, 142	HP02485	Stomach cancer	2746	334
123, 133, 143	HP02798	HT-1080	1136	267
124, 134, 144	HP10041	Saos-2	619	106
125, 135, 145	HP10246	KB	864	224
126, 136, 146	HP10392	U-2 OS	1527	258
127, 137, 147	HP10489	Stomach cancer	659	110
128, 138, 148	HP10519	Stomach cancer	710	91
129, 139, 149	HP10531	Saos-2	2182	344
130, 140, 150	HP10574	Stomach cancer	2773	428

Hereupon, the same clones as the cDNAs of the present invention can be easily obtained by screening of the cDNA libraries constructed from the human cell lines or human tissues utilized in the present invention by the use of an oligonucleotide probe synthesized on the basis of the cDNA base sequence described in any of SEQ ID Nos. 11 to 30, 41 to 60, 71 to 90, 101 to 120, and 131 to 150.

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In general, the polymorphism due to the individual difference is frequently observed in human genes. Accordingly, any cDNA in which one or plural nucleotides are inserted, deleted and/or substituted with other nucleotides in SEQ ID Nos. 11 to 30, 41 to 60, 71 to 90, 101 to 120, and

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131 to 150 shall come within the scope of the present invention.

In a similar manner, any protein in which one or plural amino acids are inserted, deleted and/or substituted with other amino acids shall come within the scope of the present invention, as far as the protein possesses the activity of any protein having the amino acid sequences represented by SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.

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The cDNAs of the present invention include cDNA fragments (10 bp or more) containing any partial base sequence in the base sequences represented by SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140 or in the base sequences represented by SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150. Also, DNA fragments consisting of a sense strand and an anti-sense strand shall come within this scope. These DNA fragments can be utilized as the probes for the genetic diagnosis.

In addition to the activities and uses described above, the polynucleotides and proteins of the present invention may exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

30 The polynucleotides provided by the present invention can be used by the research community for various purposes.

The polynucleotides can be used to express recombinant

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protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) identify chromosomes or to map related gene positions; to DNA sequences compare with endogenous in patients identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source to derive PCR primers for of information fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodiesusing DNA immunization techniques; and as an antigen to raise elicit another anti-DNA antibodies or immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can be used in interaction trap assays (such as, example, that described in Gyuris et al., Cell 75:791-803 identify polynucleotides encoding the other (1993)) to protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine

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levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

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Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be

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administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

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A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell Many protein factors discovered to date, populations. including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of The activity of a protein of the present cytokine activity. invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular

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Immunology 133:327-341, 1991; Bertagnolli, et al., J.
Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol.
152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

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proliferation and differentiation for hematopoietic and lymphopoietic cells include, 15 limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-20 1991; Moreau et al., Nature 336:690-692, Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6-In Current Protocols in Immunology. J.E.e.a. Nordan, R. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, 25 Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 -Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., 30 Giannotti, J., Clark, S.C. and Turner, K.J. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp.

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6.13.1, John Wiley and Sons, Toronto. 1991.

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Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, described in: Current limitation, those Protocols Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including combined immunodeficiency (SCID)), severe regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity other cell populations. These cells and deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial orfungal infections, or may result from autoimmune disorders. More specifically, infectious by viral, bacterial, fungal diseases causes infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp.

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and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

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Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic rheumatoid lupus erythematosus, arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia graft-versus-host disease autoimmune gravis, and Such a protein of the present inflammatory eye disease. invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. which immune suppression conditions, in desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. regulation may be in the form of inhibiting or blocking an response already in progress or may preventing the induction of an immune response. The activated T cells functions of may be inhibited suppressing T cell responses or by inducing specific Immunosuppression of T cell tolerance in T cells, or both. generally an active, non-antigen-specific, responses is process which requires continuous exposure of the T cells to Tolerance, which involves inducing the suppressive agent. non-responsiveness or anergy in T cells, is distinguishable immunosuppression in that it is generally antigenspecific and persists after exposure to the tolerizing agent

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has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

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regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), e.g., preventing high level lymphokine synthesis by activated T cells, will situations of tissue, useful in skin organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. transplants, rejection Typically, in tissue transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the The administration of a molecule which inhibits transplant. or blocks interaction of a B7 lymphocyte antigen with its immune cells (such a soluble, natural ligand(s) on as monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (e.g., B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking В lymphocyte antigen function in this matter prevents cytokine synthesis T cells, and thus acts as an immune cells, such as immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing Induction of long-term tolerance by tolerance in a subject. antigen-blocking reagents may avoid lymphocyte of repeated administration of these blocking necessity immunosuppression achieve sufficient reagents. \mathbf{To}

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

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particular blocking The efficacy of preventing organ transplant rejection or GVHD assessed using animal models that are predictive of efficacy Examples of appropriate systems which can be in humans. allogeneic cardiac grafts in rats include xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Iq fusion proteins in vivo as described in Lenschow et al., Science 257:789-792 (1992) and Turka et al., Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be to determine the effect of blocking B lymphocyte antigen function in vivo on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate Administration of reagents which block disease symptoms. T cells by disrupting receptor: ligand costimulation of interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. efficacy of blocking reagents in preventing or alleviating

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autoimmune disorders can be determined using a number of animal of human well-characterized models autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/lpr/lpr hybrid mice, murine autoimmune arthritis, diabetes mellitus in NOD mice and BB rats, and experimental myasthenia gravis (see Paul Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

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Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating be useful responses, may also in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the commoncold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells in vitro with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the in vitro activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the

transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells in vivo.

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In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. cells (e.q., sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For tumor cells obtained from a patient can example, be transfected ex vivo with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the the surface of the transfected peptides on Alternatively, gene therapy techniques can be used to target a tumor cell for transfection in vivo.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the cell provides surface of the tumor the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (e.g., a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and , microglobulin protein or an MHC class

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chain protein and an MHC class II chain protein to thereby express MHC class I or MHC class II proteins on the Expression of the appropriate class I or cell surface. class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (e.g., B7-1, B7-2, B7-3) induces a T cell mediated immune response against the Optionally, a gene encoding an transfected tumor cell. antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific Thus, the induction of a T cell mediated immune immunity. response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

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The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable for thymocyte splenocyte assays orcytotoxicity include, without limitation, those described Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., Immunol. 135:1564-1572, 1985; Takai et al., J. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J.

Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: In vitro antibody production, Mond, J.J. and Brunswick, M. In Current Protocols in Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

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Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober. Pub. Greene Publishing Associates and Interscience (Chapter 3, In Vitro assays for Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965,

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1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

5 Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 10 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992. 15

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

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A protein of the present invention may be useful in hematopoiesis and, consequently, regulation of treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells in combination with other cytokines, thereby alone or indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to

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stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation mveloid cells such as granulocytes traditional monocytes/macrophages (i.e., **CSF** activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting growth and proliferation of megakaryocytes consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the abovementioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vivo or ex-vivo conjunction ' with bone (i.e., in marrow transplantation peripheral progenitor or with cell transplantation (homologous or heterologous)) as cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and

Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, described in: Methylcellulose colony forming assays, Freshney, M.G. In Culture of Hematopoietic Cells. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. 89:5907-5911, 1992; Primitive hematopoietic colony USA forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell Ploemacher, R.E. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, Μ. Allen, T. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In Culture of Hematopoietic Cells. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

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A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is

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not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

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A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair Such agents may provide an environment attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-A protein of the invention may also be forming cells. useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair inflammation processes or by blocking orof activity, osteoclast activity, destruction (collagenase etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and

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in repairing defects to tendon or ligament tissue. De novo tissue formation induced tendon/ligament-like by composition of the present invention contributes to repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful cosmetic plastic surgery for attachment or repair of tendons The compositions of the present invention may or ligaments. provide an environment to attract tendon or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, progenitors induce differentiation of of tendonligament-forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect The compositions of the invention may also tissue repair. be useful in the treatment of tendinitis, carpal tunnel ligament defects. The syndrome and other tendon or compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

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The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, i.e. for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve More specifically, a protein may be used in the tissue. treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy localized neuropathies, and central nervous system diseases, such Alzheimer's, Parkinson's disease, Huntington's lateral sclerosis, and Shy-Drager disease, amyotrophic be treated Further conditions which may syndrome. accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head

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trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

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It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon);

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International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

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A protein of the present invention may also exhibit inhibin-related activities. Inhibins or characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of Thus, a protein of the follicle stimulating hormone (FSH). present invention, alone or in heterodimers with a member of the inhibin family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among

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other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) including, for example, monocytes, mammalian cells, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma tissues, as well as in treatment of localized infections. attraction of lymphocytes, monocytes example, For neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among

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other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. J. of 25: 1744-1748; Gruber et al. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (includinghereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include,

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without limitation, those described in: Linet et al., J. 26:131-140, 1986; Burdick Clin. Pharmacol. et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

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A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors cell-cell interactions and their (including without limitation, cellular adhesion molecules selectins, integrins and their ligands) receptor/ligand involved in antigen presentation, pairs antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful screening of potential peptide or small inhibitors of the relevant receptor/ligand interaction. invention (including, protein of the present and limitation, fragments of receptors ligands) inhibitors of receptor/ligand themselves be useful as interactions.

25 The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22),

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Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

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Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cellcell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of ytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A

protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth

Other Activities

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A protein of the invention may also exhibit one or more following additional activities or inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body shape (such as, for example, size oraugmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting fertility of male or female subjects; the effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of

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embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

Examples

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The present invention is specifically illustrated in more detail by the following Examples, but Examples are not intended to restrict the present invention. The basic operations with regard to the recombinant DNA and the enzymatic reactions were carried out according to the literature ["Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory, 1989]. Unless otherwise stated, restrictive enzymes and a variety of modification enzymes to be used were those available from Takara Shuzo. The buffer compositions and the reaction conditions for each of the enzyme reactions were as described in the manufacturer's instructions. The cDNA synthesis was carried out according to the literature [Kato, S. et al., Gene 150: 243-250 (1994)].

(1) Selection of cDNAs Encoding Proteins Having Hydrophobic Domains

The cDNA library of fibrosarcoma cell line HT-1080 (WO98/11217), the cDNA library of osteosarcoma cell line Saos-2 (WO97/33993), the cDNA library of osteosarcoma cell line U-2 OS (WO98/21328), the cDNA library of epidermoid

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carcinoma cell line KB (WO98/11217), the cDNA library of stomach cancer delivered by the operation (WO98/21328), the cDNA library of liver tissue delivered by the operation (WO98/21328), and were used for the cDNA libraries. Full-length cDNA clones were selected respective libraries and the whole base sequences thereof were determined to construct a homo-protein cDNA consisting of the full-length CDNA clones. The hydrophobicity/hydrophilicity profiles were determined for by the full-length cDNA proteins encoded registered in the homo-protein cDNA bank by the Kyte-Doolittle method [Kyte, J. & Doolittle, R. F., J. Mol. Biol. 157: 105-132 (1982)] to examine the presence or absence of a hydrophobic region. Any clone that has a hydrophobic region being putative as a secretory signal or a transmembrane domain in the amino acid sequence of the encoded protein was selected as a clone candidate.

(2) Protein Synthesis by In Vitro Translation

The plasmid vector bearing the cDNA of the present invention was used for in vitro transcription/translation with a T_uT rabbit reticulocyte lysate kit (Promega). In this case, [35] methionine was added to label the expression product with a radioisotope. Each of the reactions was carried out according to the protocols attached to the kit. Two micrograms of the plasmid was subjected to the reaction at 30°C for 90 minutes in the reaction solution of a total volume of 25 μ l containing 12.5 μ l μ of T_NT rabbit reticulocyte lysate, 0.5 μ l of a buffer solution (attached the kit), 2 μ l of an amino acid mixture (without methionine), 2 μ l of [35]methionine (Amersham) (0.37 MBq/ μ l), 0.5 μ l of T7 RNA polymerase, and 20 U of RNasin. Also, an experiment in the presence of a membrane system was carried

out by adding to this reaction system 2.5 μ l of a canine pancreas microsome fraction (Promega). To 3 μ l of the resulting reaction solution was added 2 μ l of the SDS sampling buffer (125 mM Tris-hydrochloric acid buffer, pH 6.8, 120 mM 2-mercaptoethanol, 2% SDS solution, 0.025% bromophenol blue, and 20% glycerol) and the resulting mixture was heated at 95°C for 3 minutes and then subjected to SDS-polyacrylamide gel electrophoresis. The molecular weight of the translation product was determined by carrying out the autoradiography.

(3) Expression by COS7

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Escherichia coli cells bearing the expression vector for the protein of the present invention was incubated at 37°C for 2 hours in 2 ml of the 2xYT culture medium containing $100~\mu\text{g/ml}$ of ampicillin, the helper phage M13KO7 $(50~\mu\text{l})$ was added, and the incubation was continued at 37°C overnight. A supernatant separated by centrifugation underwent precipitation with polyethylene glycol to obtain single-stranded phage particles. These particles were suspended in $100~\mu\text{l}$ of 1 mM Tris-0.1 mM EDTA, pH 8 (TE).

The cultured cells derived from simian kidney, COS7, were incubated at 37°C in the presence of 5% CO₂ in the Dulbecco's modified Eagle's culture medium (DMEM) containing 10% fetal calf serum. Into a 6-well plate (Nunc, well diameter: 3 cm) were inoculated with 1 x 10^5 COS7 cells and incubation was carried out at 37°C for 22 hours in the presence of 5% CO₂. After the culture medium was removed, the cell surface was washed with a phosphate buffer solution and then washed again with DMEM containing 50 mM Trishydrochloric acid (pH 7.5) (TDMEM). To the resulting cells was added a suspension of 1 μ l of the single-stranded phage suspension, 0.6 ml of the DMEM culture medium, and 3 μ l of

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TRANSFECTAM™ (IBF) and the resulting mixture was incubated at 37°C for 3 hours in the presence of 5% CO2. After the sample solution was removed, the cell surface was washed with TDMEM, 2 ml per well of DMEM containing 10% fetal calf serum was added, and the incubation was carried out at 37°C for 2 days in the presence of 5% CO2. After the culture was replaced by a culture medium medium [35S]cystine or [35S]methionine, the incubation was carried out for one hour. After the culture medium and the cells were separated by centrifugation, proteins in the culture fraction the cell-membrane fraction medium and subjected to SDS-PAGE.

(4) Clone Examples
<HP01550> (SEQ ID Nos. 1, 11, and 21)

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Determination of the whole base sequence of the cDNA insert of clone HP01550 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 65-bp 5'-untranslated region, a 378-bp ORF, and a 67-bp 3'untranslated region. The ORF codes for a protein consisting of 125 amino acid residues and there existed one putative Figure 1 depicts domain. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of 15 kDa that was almost identical with the molecular weight of 13,825 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein F45G2.c (GenBank Accession No. Z93382). Table 2 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C.

elegans hypothetical protein F45G2.c (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.5% in the entire region.

Table 2

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA338859) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02593> (SEQ ID Nos. 2, 12, and 22)

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Determination of the whole base sequence of the cDNA insert of clone HP02593 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 103-bp 5'-untranslated region, a 396-bp ORF,

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and a 198-bp 3'-untranslated region. The ORF codes for a protein consisting of 131 amino acid residues and there existed four putative transmembrane domains at the C-terminus. Figure 2 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of a high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to a human OB-R gene-related protein (EMBL Accession No. Y12670). Table 3 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human OB-R gene-related protein (OB). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 67.9% in the entire region.

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Table 3

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA306490) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10195> (SEQ ID Nos. 3, 13, and 23)

Determination of the whole base sequence of the cDNA insert of clone HP10195 obtained from cDNA library of human fibrosarcoma HT-1080 revealed the structure consisting of a 286-bp 5'-untranslated region, a 729-bp ORF, and a 604-bp region. The ORF codes for 3'-untranslated consisting of 242 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 3 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. vitro translation resulted in formation of a translation larger product of 32 kDa that was somewhat molecular weight of 27,300 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed the registration of sequences that were similar to the Aplysia VAP-33 (SWISS-PROT Accession No. P53173). Table 4 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the Aplysia VAP-33 (AP). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the

present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 46.5% in the entire region.

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Table 4

HP MAKHEQILVLDPPTDLKFKGPFTDVVTTNLKLRNPSDRKVCFKVKTTAPRRYCVRPNSGI **.*** *.*...*.********************* AP MASHEQALILEPAGELRFKGPFTDVVTADLKLSNPTDRRICFKVKTTAPKRYCVRPNSGI 10 HP IDPGSTVTVSVMLQPFDYDPNEKSKHKFMVQTIFAPPNTSD-MEAVWKEAKPDELMDSKL AP LEPKTSIAVAVMLQPFNYDPNEKNKHKFMVQSMYAPDHVVESQELLWKDAPPESLMDTKL HP RCVFEMPNENDKLNDMEPSK-----AVPLNASKQDGPMPKP-HSVSLNDTE 15 AP RCVFEMPDGSHQAPASDASRATDAGAHFSESALEDPTVASRKTETQSPKRVGAVGSAGED HP TRKLMEECKRLQGEMMKLSEENRHLRDEGLRLRKVAHSD--KPGSTSTASFRDNVTSPLP AP VKKLQHELKKAQSEITSLKGENSQLKDEGIRLRKVAMTDTVSPTPLNPSPAPAAAVRAFP 20 HP SLLVVIAAIFIGFFLGKFIL ... *.***..*..* AP PVVYVVAAIILGLIIGKFLL

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA447905) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10423> (SEQ ID Nos. 4, 14, and 24)

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Determination of the whole base sequence of the cDNA insert of clone HP10423 obtained from cDNA library of human osteosarcoma cell line U-2 OS revealed the consisting of a 64-bp 5'-untranslated region, a 795-bp ORF. and a 207-bp 3'-untranslated region. The ORF codes for a protein consisting of 264 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane domain at the N-terminus. Figure 4 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 30 kDa that was almost identical with the molecular weight of 29,377 predicted from the ORF. When expressed in COS7 cells, an expression product of about 31 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D80116) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10506> (SEQ ID Nos. 5, 15, and 25)

Determination of the whole base sequence of the cDNA insert of clone HP10506 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 53-bp 5'-untranslated region, a 339-bp ORF, and a 226-bp 3'-untranslated region. The ORF codes for a protein consisting of 112 amino acid residues and there existed one putative transmembrane domain. Figure 5 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-

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Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,821 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA282544) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10507> (SEQ ID Nos. 6, 16, and 26)

Determination of the whole base sequence of the cDNA insert of clone HP10507 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 412-bp 5'-untranslated region, a 441-bp ORF, and a 168-bp 3'untranslated region. The ORF codes for a protein consisting of 146 amino acid residues and there existed a secretory signal at the N-terminus and one putative transmembrane 6 C-terminus. Figure domain at the hydrophobicity/hydrophilicity profile, obtained by the Kyteprotein. Doolittle method, of the present translation resulted in formation of a translation product of 19 kDa that was somewhat larger than the molecular weight of 16,347 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA424759) in ESTs, but, since they

are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

5 <HP10548> (SEQ ID Nos. 7, 17, and 27)

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Determination of the whole base sequence of the cDNA insert of clone HP10548 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 330-bp 5'-untranslated region, a 1035-bp ORF, and a 67-bp 3'untranslated region. The ORF codes for a protein consisting of 344 amino acid residues and there existed four putative Figure 7 depicts domains. transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kytepresent protein. Doolittle method, of the translation resulted in formation of a translation product of a high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA143152) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

25 <HP10566> (SEQ ID Nos. 8, 18, and 28)

Determination of the whole base sequence of the cDNA insert of clone HP10566 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 61-bp 5'-untranslated region, a 294-bp ORF, and a 246-bp 3'-untranslated region. The ORF codes for a protein consisting of 97 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 8 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,452 predicted from the ORF. When expressed in COS7 cells, an expression product of about 12 kDa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W79821) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10567> (SEQ ID Nos. 9, 19, and 29)

Determination of the whole base sequence of the cDNA insert of clone HP10567 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 77-bp 5'-untranslated region, a 375-bp ORF, and a 133-bp 3'untranslated region. The ORF codes for a protein consisting of 124 amino acid residues and there existed one putative transmembrane domain at the C-terminus. Figure 9 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 14 kDa that was almost identical with the molecular weight of 14,484 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA428475) in ESTs, but, since they

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are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

5 <HP10568> (SEQ ID Nos. 10, 20, and 30)

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Determination of the whole base sequence of the cDNA insert of clone HP10568 obtained from cDNA library of the human stomach cancer revealed the structure consisting of a 56-bp 5'-untranslated region, a 984-bp ORF, and a 60-bp 3'untranslated region. The ORF codes for a protein consisting of 327 amino acid residues and there existed a secretory at the N-terminus and one putative transmembrane signal the C-terminus. Figure 10 depicts domain hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of 36.5 kDa that was almost identical with the molecular weight of 34,326 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 40 kDa which is considered to have a sugar chain being addition, there exist in the amino In sequence of this protein two sites at which N-qlycosylation may occur (Asn-Leu-Thr at position 138 and Asn-Leu-Ser at position 206). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory sequence, allows to expect that the mature protein starts from valine at position 24. When expressed in COS7 cells, an expression product of about 31 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein has revealed that the protein was similar to the human cell-surface A33 antigen

(SWISS-PROT Accession No. Q99795). Table 5 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human cell-surface A33 antigen (A3). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 30.0% in the N-terminal region of 243 residues.

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Table 5

HP MAELPGPFLCGALLGFLCLSGLAVEVKVPTEPLSTPLGKTAELTCTYSTSVGDSFAL-EW MVGKMWPVLWTLCAVRVTVDAISVETPQDVLRASQGKSVTLPCTYHTSTSSREGLIQW 15 **A3** HP SFVQPGKPISESHPILYFTNGHLYPTGSKSKRVSLLQNPPTVGVATLKLTDVHPSDTGTY * * * * * * * * . A3 DKLL--LTHTERVVIWPFSNKN-YIHGELYKNRVSISNNAEQSDASITIDQLTMADNGTY HP LCQVNNPPDFYTNGLGLINLTVLVPPSNPLCSQSGQTSVGGSTALRCSSSEGAPKPVYNW * *. .*. .*. . .* ****** *. .*. * .*. .* * *.*. *.* 20 A3 ECSVSLMSDLEGNTKSRVRLLVLVPPSKPECGIEGETIIGNNIQLTCQSKEGSPTPOYSW HP VRLGTFPTPSPGSMVQDEVSGQLILTNLSLTSSGTYRCVATNQMGSASCELTLSVTEPS-A3 KRYNILNOEOP--LAQPASGQPVSLKNISTDTSGYYICTSSNEEGTQFCNITVAVRSPSM HP -QGRVAGALIGVLLGVLLLSVAAFCLVRFQKERGKKPKETYGGSDLREDAIAPGISEHTC 25 .**.* A3 NVALYVGIAVGVVAALIIIGIIIYCCCCRGKDDNTEDKEDARPNREAYEEPPEQLRELSR HP MRADSSKGFLERPSSASTVTTTKSKLPMVV 30 A3 EREEEDDYRQEEQRSTGRESPDHLDQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration

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of sequences that shared a homology of 90% or more (for example, Accession No. T24595) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01426> (SEQ ID Nos. 31, 41, and 51)

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Determination of the whole base sequence of the cDNA insert of clone HP01426 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 1-bp 5'-untranslated region, a 942-bp ORF, and a 122-bp untranslated region. The ORF codes for a protein consisting of 313 amino acid residues and there existed a putative depicts Figure 11 signal. hydrophobicity/hydrophilicity profile, obtained by the Kytepresent protein. method, of the translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 34,955 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 38 kDa which is considered to have a sugar chain being attached after secretion. In addition, there exists in the amino acid sequence of this protein one site at which Nglycosylation may occur (Asn-Ser-Ser at position 163). Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from tryptophan at position 17. When expressed in COS7 cells, an expression product of about 39 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the

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protein was similar to the Xenopus laevis cortical granule lectin (EMBL Accession No. X82626). Table 6 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the X. laevis cortical granule lectin (XL). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 67.9% in the region other than the N-terminal region.

Table 6

HP MNOLSFLLFLIATTRGWSTDEANTYFKEWTCSSSPSLPRSCKEIKDECPSAFDGLYFLRT ******* . * **.* * . 15 XL MLVHILLLVTGGLSQSCEPVVIVASKNMVKQLDCDKFRSCKEIKDSNEEAQDGIYTLTS HP ENGVIYQTFCDMTSGGGGWTLVASVHENDMRGKCTVGDRWSSQQGSKADYPEGDGNWANY ..*. *******..********** XL SDGISYQTFCDMTTNGGGWTLVASVHENNMAGKCTIGDRWSSQQGNRADYPEGDGNWANY HP NTFGSAEAATSDDYKNPGYYDIQAKDLGIWHVPNKSPMQHWRNSSLLRYRTDTGFLQTLG 20 XL NTFGSAGGATSDDYKNPGYYDIEAYNLGVWHVPNKTPLSVWRNSSLQRYRTTDGILFKHG HP HNLFGIYQKYPVKYGEGKCWTDNGPVIPVVYDFGDAQKTASYYSPYGQREFTAGFVQFRV ***..*. ***** *.* .*.******.*.*.*** XL GNLFSLYRIYPVKYGIGSCSKDSGPTVPVVYDLGSAKLTASFYSPDFRSQFTPGYIOFRP 25 HP FNNERAANALCAGMRVTGCNTEHHCIGGGGYFPEASPQQCGDFSGFDWSGYGTHVGYSSS XL INTEKAALALCPGMKMESCNVEHVCIGGGGYFPEADPRQCGDFAAYDFNGYGTKKFNSAG HP REITEAAVLLFYR ****** 30 XL IEITEAAVLLFYL

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R06009) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02515> (SEQ ID Nos. 32, 42, and 52)

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Determination of the whole base sequence of the cDNA insert of clone HP02515 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the consisting of a 176-bp 5'-untranslated region, a 690-bp ORF. and a 71-bp 3'-untranslated region. The ORF codes for a protein consisting of 229 amino acid residues and there existed a putative secretory signal at N-terminus and one putative transmembrane domain at the C-terminus. Figure 12 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. vitro translation resulted in formation of a translation product of 27 kDa that was almost identical with the molecular weight of 26,000 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 25.5 kDa from which the secretory signal considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from phenylalanine at position 28.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human T1/ST2 receptor binding protein (GenBank Accession No. U41804). Table 7 shows the

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comparison between amino acid sequences of the human protein of the present invention (HP) and the human T1/ST2 receptor binding protein (T1). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 55.8% in the entire region.

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Table 7

T1 AFEARDRNLQEGNLERVNFWSAVNVAVLLLVAVLQVCTLKRFFQDKRPVPT

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA381943) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02575> (SEQ ID Nos. 33, 43, and 53)

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Determination of the whole base sequence of the cDNA insert of clone HP02575 obtained from cDNA library of human Saos-2 osteosarcome cell line revealed the consisting of a 55-bp 5'-untranslated region, a 1404-bp ORF, and a 219-bp 3'-untranslated region. The ORF codes for a protein consisting of 467 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 13 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the protein. In vitro translation resulted in formation of a translation product of 52 kDa that was almost identical with the molecular weight of 54,065 predicted from the ORF. this case, the addition of a microsome led to the formation of a product of 57 kDa which is considered to have a sugar chain being attached afetr secretion. In addition, there exist in the amino acid sequence of this protein three sites at which N-qlycosylation may occur (Asn-Arg-Thr at position 171, Asn-Ser-Thr at position 239 and Asn-Asp-Thr at position Application of the (-3,-1) rule, а method predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from histidine at position 29. When expressed in COS7 cells, an expression product of about 55 kDa was observed in the supernatant fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human α -L-fucosidase (SWISS-PROT Accession No. P04066). Table 8 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human α -L-fucosidase (FC). Therein,

the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.8% in the entire region.

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Table 8

	HP	${\tt MRPQELPRLAFPLLLLLLLLPPPPC-PAHSATRFDPTWESLDARQLPAWFDQAKFGIFI}$
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	FC	MRSRPAGPALLLLLLFLGAAESVRRAQPPRRYTPDWPSLDSRPLPAWFDEAKFGVFI
	HP	HWGVFSVPSFGSEWFWWYWQKEKIPKYVEFMKDNYPPSFKYEDFGPLFTAKFFNANQWAD
		******* * * * * * * * * * * * * * *
	FC	HWGVFSVPAWGSEWFWWHWQGEGRPQYQRFMRDNYPPGFSYADFGPQFTARFFHPEEWAD
15	HP	IFQASGAKYIVLTSKHHEGFTLWGSEYSWNWNAIDEGPKRDIVKELEVAIRNRTDLRFGL
		.***.***.***.***
	FC	LFQAAGAKYVVLTTKHHEGFTNWPSPVSWNWNSKDVGPHRDLVGELGTALRKR-NIRYGL
	HP	YYSLFEWFHPLFLEDESSSFHKRQFPVSKTLPELYELVNNYQPEVLWSDGDGGAPDQYWN
		*.**.***** ** .**.***.**.**.*** ** **
20	FC	YHSLLEWFHPLYLLDKKNGFKTQHFVSAKTMPELYDLVNSYKPDLIWSDGEWECPDTYWN
	HP	STGFLAWLYNESPVRGTVVTNDRWGAGSICKHGGFYTCSDRYNPGHLLPHKWENCMTIDK
		..***.** * **** *
	FC	STNFLSWLYNDSPVKDEVVVNDRWGQNCSCHHGGYYNCEDKFKPQSLPDHKWEMCTSIDK
	HP	${\tt LSWGYRREAGISDYLTIEELVKQLVETVSCGGNLLMNIGPTLDGTISVVFEERLRQMGSW}$
25		.*****
	FC	FSWGYRRDMALSDVTEESEIISELVQTVSLGGNYLLNIGPTKDGLIVPIFQERLLAVGKW
	HP	LKVNGEAIYETHTWRSQNDTVTPDVWYTSKPKEKLVYAIFLKWPTSGQLFLGHPKAILGA
		****** * ***** ****** *****
	FC	LSINGEAIYASKPWRVQWEKNTTSVWYTSKGSAVYAIFLHWPENGVLNLESPITT-ST
30	HP	TEVKLLGHGQPLNWISLEQNGIMVELPQLTIHQMPCKWGWALALTNVI
		*** *.****
	FC	TKITMLGIQGDLKWSTDPDKGLFISLPQLPPSAVPAEFAWTIKLTGVK

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N28668) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

10 <HP10357> (SEQ ID Nos. 34, 44, and 54)

Determination of the whole base sequence of the cDNA insert of clone HP10357 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 113-bp 5'-untranslated region, a 300-bp ORF, and a 54-bp untranslated region. The ORF codes for a protein consisting of 99 amino acid residues and there existed two putative transmembrare domains. Figure 14 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 11 kDa that was almost identical with the molecular weight of 10,923 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA477156) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10447> (SEQ ID Nos. 35, 45, and 55)

Determination of the whole base sequence of the cDNA

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insert of clone HP10447 obtained from cDNA library of human liver revealed the structure consisting of a 271-bp 5'untranslated region, а 570-bp ORF, and a untranslated region. The ORF codes for a protein consisting of 189 amino acid residues and there existed five putative transmembrare domains. Figure 15 depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA296976) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10477> (SEQ ID Nos. 36, 46, and 56)

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20 Determination of the whole base sequence of the cDNA insert of clone HP10477 obtained from cDNA library of human liver revealed the structure consisting of a 149-bp 5'untranslated region, a 1092-bp ORF, and 15-bp a untranslated region. The ORF codes for a protein consisting 25 of 363 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 16 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product 30 of 40 kDa that was almost identical with the molecular weight of 39,884 predicted from the ORF.

The search of the protein data base using the amino

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acid sequence of the present protein revealed that the protein was similar to the human peptidoglycan recognition protein (GenBank Accession No. AF076483). Table 9 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human peptidoglycan recognition protein (PG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 54.8% in the entire region.

Table 9

HP MVDSLLAVTLAGNLGLTFLRGSQTQSHPDLGTEGCWDQLSAPRTFTLLDPKASLLTKAFL

HP NGALDGVILGDYLSRTPEPRPSLSHLLSQYYGAGVARDPGFRSNFRRQNGAALTSASILA

HP QQVWGTLVLLQRLEPVHLQLQCMSQEQLAQVAANATKEFTEAFLGCPAIHPRCRWGAAPY

PG MSRRSMLLAWALPSLLRLGAAQETEDPACCSPIVPRNEWKALA-

.. ** * * .

HP RGRPKLLQLPLGFLYVHHTYVPAPPCTDFTRCAANMRSMQRYHQDTQGWGDIGYSFVVGS

PG SECAQHLSLPLRYVVVSHT--AGSSCNTPASCQQQARNVQHYHMKTLGWCDVGYNFLIGE

HP DGYVYEGRGWHWVGAHTLGH-NSRGFGVAIVGNYTAALPTEAALRTVRDTLPSCAVRAGL

PG DGLVYEGRGWNFTGAHSGHLWNPMSIGISFMGNYMDRVPTPQAIRAAOGLL-ACGVAOGA

HP LRPDYALLGHRQLVRTDCPGDALFDLLRTWPHFTATVKPRPARSVSKRSRREPPPRTLPA
**..*. ** ... ** ... **...

PG LRSNYVLKGHRDVORTLSPGNOLYHLIONWPHYRSP

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration

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of sequences that shared a homology of 90% or more (for example, Accession No. AA424759) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10513> (SEQ ID Nos. 37, 47, and 57)

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Determination of the whole base sequence of the cDNA insert of clone HP10513 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 134-bp 5'-untranslated region, a 750-bp ORF, and a 0-bp 3'-untranslated region. The ORF codes for a protein consisting of 249 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 17 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 29 kDa that was almost identical with the molecular weight of 27,373 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0512 (GenBank Accession No. AB011084). Table 10 shows the comparison between amino acid sequences of the human invention protein of the present (HP) and the hypothetical protein KIAA0512 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 31.6% in the C-terminal region of 196 amino acid residues.

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Table 10

MGGPRGAGWVAAGLLLGAGACYCIYRLTRGRRRG HP 5 KI RGRGRRPVAMOKRPFPYEIDEILGVRDLRKVLALLQKSDDPFIQQVALLTLSNNANYSCN HP DRELGIRSSKSAEDLTDGSYDDVLNAEQLQKLLYLLESTEDPVIIERALITLGNNAAFSV * * . * . . KI QETIRKLGGLPIIANMINKTDPHIKEKALMAMNNLSENYENQGRLQVYMNKVMDDIMASN 10 HP NQAIIRELGGIPIVANKINHSNQSIKEKALNALNNLSVNVENQIKIKVQVLKLLLNLSEN*... * ****..**.* *..** KI LNSAVQVVGLKFLTNMTITNDYQHLLVNSIANF--FRLLSQGGGKIKVEILKILSNFAEN HP PAMTEGLLRAQVDSSFLSLYDSHVAKEILLRVLTLFQNIKNCLKIEGHLAVQPTFTEGSL *.* . **..** .** ***.*...***.. * . *. * 15 KI PDMLKKLLSTOVPASFSSLYNSYVESEILINALTLFEIIYDNLRAE--VFNYREFNKGSL HP FFL-LHGEECAQKIRALVDHHDAEVKEKVVTIIPKI *.* .. *..****..*** ** **... *. KI FYLCTTSGVCVKKIRALANHHDLLVKVKVIKLVNKF

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N92228) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10540> (SEQ ID Nos. 38, 48, and 58)

Determination of the whole base sequence of the cDNA insert of clone HP10540 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 47-bp 5'-untranslated region, a 297-bp ORF, and a 245-bp 3'-untranslated region. The ORF codes for a protein consisting of 98 amino acid residues and there existed two putative transmembrane domains. Figure 18 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein similar was to the Caenorhabditis hypothetical protein CEF49C12.12 (GenBank Accession Z68227). Table 11 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein CEF49C12.12 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 36.1% in the entire region.

Table 11

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CE MGKICPLMGPKMSAFCMVMSVWGVIFLGLLGVFFYIQAVTLFPDLHF-EGHGKVPSSVID HP NLYEQVSYNCFIAAGLYLLLGGFSFCQVRLNKRKEYMVR

[•]

³⁰ CE AKYNEKATQCWIAAGLYAVTLIAVFWQ---NKYNTAQIF

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA420715) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

10 <HP10557> (SEQ ID Nos. 39, 49, and 59)

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Determination of the whole base sequence of the cDNA insert of clone HP10557 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 24-bp 5'-untranslated region, a 519-bp ORF, and a 130-bp 3'untranslated region. The ORF codes for a protein consisting of 172 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 19 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 32 kDa that was larger than the molecular weight of 18,844 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 39 kDa which is considered to have been subjected to modification after secretion. In addition, there exist in the amino acid sequence of this protein no site at which Nglycosylation may occur. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 32. When expressed in COS7 cells, an expression product of about 20 kDa was observed in the supernatant fraction and the membrane fraction.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human progesterone binding protein (EMBL Accession No. AJ002030). Table 12 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human progesterone binding protein (PG). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 30.5% in the C-terminal region of 151 amino acid residues.

Table 12

15 HP **MVGPAP** PG MAAGDGDVKLGTLGSGSESSNDGGSESPGDAGAAAEGGGWAAAALALLTGGGEMLLNVAL HP RRRLRPLAALALVLALAPGLPTARAGQTPRPAERGPPV--RLFTEEELARYGGEEEDQPI 20 PG VALVLLGAYRLWVRWGRRGLGAGAGAGEESPATSLPRMKKRDFSLEQLRQYDG-SRNPRI HP YLAVKGVVFDVTSGKEFYGRGAPYNALTGKDSTRGVAKMSLDPADLTHDTTGLTAKELEA ***.* *****.*..**...**...**...* PG LLAVNGKVFDVTKGSKFYGPAGPYGIFAGRDASRGLATFCLDKDALRDEYDDLSDLNAVQ 25 HP LDEV--FTKVYKAKYPIVGYTARRILNEDGSPNLDFKPEDQPHFDIKDEF*.** PG MESVREWEMQFKEKY---DYVG-RLLKPGEEPS-EYTDEEDTKDHNKQD

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

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example, Accession No. AA101709) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10563> (SEQ ID Nos. 40, 50, and 60)

Determination of the whole base sequence of the cDNA insert of clone HP10563 obtained from cDNA library of human Saos-2 osteosarcoma cell line revealed the consisting of a 126-bp 5'-untranslated region, a 363-bp ORF, and a 936-bp 3'-untranslated region. The ORF codes for a protein consisting of 120 amino acid residues and there existed two putative transmembrane domains. depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 18.5 kDa that was larger than the molecular weight of 13,180 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical protein F27F23.15 (GenBank Accession No. AC003058). Table 13 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the A. thaliana hypothetical protein F27F23.15 (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.5% in the entire region.

Table 13

AT VLGFFMAYNRVG-GDRGHGIFFIVLGCLLFIPGFYYTRIAYYAYKGYKGFSFSNIPSV

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA083574) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01467> (SEQ ID Nos. 61, 71, and 81)

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Determination of the whole base sequence of the cDNA insert of clone HP01467 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 65-bp 5'-untranslated region, a 924-bp ORF, and a 447-bp 3'-untranslated region. The ORF codes for a protein consisting of 307 amino acid residues and there existed three putative transmembrane domains. Figure 21 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino

acid sequence of the present protein revealed that the protein was similar to the rat Sec22 homologue (GenBank Accession No. U42209). Table 14 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat Sec22 homologue (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 94.6% in the N-terminal region of 241 amino acid residues. The protein of the present invention was longer by 53 amino acids at the C-terminus than the rat Sec22 homologue.

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Table 14

RN QMICLCLQGRKERT

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA421925) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01956> (SEQ ID Nos. 62, 72, and 82)

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Determination of the whole base sequence of the cDNA insert of clone HP01956 obtained from cDNA library of human liver revealed the structure consisting of a 86-bp untranslated region, 552-bp ORF, and a 359-bp а untranslated region. The ORF codes for a protein consisting of 183 amino acid residues and there existed one putative transmembrane domain. Figure 22 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In translation resulted in formation of a translation product of 20.5 kDa that was almost identical with the molecular weight of 20,073 predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the yeast hypothetical protein 21.5 kDa (SWISS-PROT Accession No. P53073). Table 15 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the yeast hypothetical protein 21.5 kDa (SC). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology

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of 34.3% in the C-terminal region of 108 amino acid residues.

Table 15

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA159753) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02545> (SEQ ID Nos. 63, 73, and 83)

Determination of the whole base sequence of the cDNA insert of clone HP02545 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 133-bp 5'-untranslated region, a 984-bp ORF, and a 636-bp 3'-untranslated region. The ORF codes for a

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protein consisting of 327 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain at the C-terminus. Figure 23 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat embigin (EMBL Accession No. AJ009698). Table 16 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat embigin (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 65.4% in the entire region.

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Table 16

HP MRALPGLLEARARTPRLLLLQCLLAAARPSSADGSAPDSPFTSPPLREEIMAN--NFSLE 5 RN MRSHTGLRALVAPGCSLLLL-YLLAATRPDRAVGDPADSAFTSLPVREEMMAKYANLSLE HP SHNISLTEHSSMPVEKNITLERPSNVNLTCQFTTSGDLNAVNVTWKKDGEQLE--NNYLV ..******... *.*******...*. **...*. ...** ... ** RN TYNISLTEQTRVS-EQNITLERPSHLELECTFTATEDVMSMNVTWKKDDALLETTDGFNT HP SATGSTLYTQYRFTIINSKOMGSYSCFFREEKEQRGTFNFKVPELHGKNKPLISYVGDST 10 *.***.*****..*****..** RN TKMGDTLYSQYRFTVFNSKQMGKYSCFLGEE--LRGTFNIRVPKVHGKNKPLITYVGDST HP VLTCKCQNCFPLNWTWYSSNGSVKVPVGVQM-NKYVINGTYANETKLKITQLLEEDGESY **.*.*****.***** ***...**...*. ** ***...* RN VLKCECONCLPLNWTWYMSNGTAOVPIDVHVNDKFDINGSYANETKLKVKHLLEEDGGSY 15 HP WCRALFOLGESEEHIELVVLSYLVPLKPFLVIVAEVILLVATILLCEKYTOKKKKHSDEG RN WCRAAFPLGESEEHIKLVVLSFMVPLKPFLAIIAEVILLVAIILLCEVYTOKKKNDPDDG HP KEFEQIEQLKSDDSNGIENNVPRHRKNESLGQ ************* 20 RN KEFEQIEOLKSDDSNGIENNVPRYRKTDSGDQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA312629) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02551> (SEQ ID Nos. 64, 74, and 84)

Determination of the whole base sequence of the cDNA insert of clone HP02551 obtained from cDNA library of human

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line Saos-2 revealed the cell osteosarcoma consisting of a 61-bp 5'-untranslated region, a 672-bp ORF. and a 384-bp 3'-untranslated region. The ORF codes for a protein consisting of 223 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 24 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 27 kDa that was somewhat larger than the molecular weight of 24,555 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 26 kDa from which the secretory signal is considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glutamine at position 20.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse FGF binding protein U49641). Table 17 No. Accession (GenBank comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse FGF binding protein (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 21.2% in the entire region other than the N-terminal region. In particular, all the eight cysteine residues contained in the both proteins were conserved.

Table 17

HP MKFVPCLLLVTLSCLGTLGQAPRQKQGST 5 MM MRLHSLILLSFLLLATOAFSEKVRKRAKNAPHSTAEEGVEGSAPSLGKAONKORSRTSKS HP GEEFHFQTGGRDSCTMRPSSLGQGAGEVWLRVDCRNTDQTYWCEYRGQPSMCQAFAADPK MM LTHGKFVTKDQATC---RWAVTEEEQGISLKVQCTQADQEFSCVFAGDPTDCLKHDKD-Q HP SYWNOALOELRRLHHACQGA-PVLRPSVCREAGPQAHMQQVTSSLKGSPEPNQOPEAGTP 10 MM IYWKOVARTLRKOKNICRDAKSVLKTRVCRKRFPESNLKLVNPNARGNTKPRKEKAEVSA HP SLRPKATVKLTEATOLGKDSMEELGKAKPTTRPTAKPTQPGPRPGGNEEAKKKAWEHCWK *... .*. * . *. * . . . MM REHNKVOEAVSTEPNRIKEDI-TLNPAATOTM-TIRDPECLEDPDVLNQ-RKTALEFCGE 15 HP PFQALCAFLISFFRG*.*..... MM SWSSICTFFLNMLQATSC

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA317400) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02631> (SEQ ID Nos. 65, 75, and 85)

Determination of the whole base sequence of the cDNA insert of clone HP02631 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 42-bp 5'-untranslated region, a 147-bp ORF,

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and a 1191-bp 3'-untranslated region. The ORF codes for a protein consisting of 48 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 25 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa or less.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA156969) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02632> (SEQ ID Nos. 66, 76, and 86)

Determination of the whole base sequence of the cDNA insert of clone HP02632 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 50-bp 5'-untranslated region, a 1116-bp ORF, and a 337-bp 3'-untranslated region. The ORF codes for a protein consisting of 371 amino acid residues and there existed eight putative transmembrane domains. Figure 26 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis elegans hypothetical protein CELC2H12 (GenBank Accession No. U23169). Table 18 shows the comparison between amino acid sequences

of the human protein of the present invention (HP) and the C. elegans hypothetical protein CELC2H12 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 51.4% in the entire region.

Table 18

10 HP MAWTKYQLFLAGLMLVTGSINTLSAKWADNFMAEGCGGSKEHSFQHPFLQAVGMFLGEFS * . * * * * * . . . * * * * * * . . .*.***** **. **. MVAFAVIISVMMVVTGSLNTICAKWADSIKAD-----GVPFNHPFLQATCMFFGEFL HP CLAAFYL-----LRCRAAGQSDS-----SVDPQQPFNPLLFLPPALCDMTGTSL 15 * ...*.*.* CE CLVVFFLIFGYKRYVWNRANVQGESGSVTEITSEEKPTLPPFNPFLFFPPALCDILGTSI HP MYVALNMTSASSFQMLRGAVIIFTGLFSVAFLGRRLVLSQWLGILATIAGLVVVGLADLL **..**.*.********** .*.*.*. .. ***.**..*. CE MYIGLNLTTASSFQMLRGAVIIFTGLLSVGMLNAQIKPFKWFGMLFVMLGLVIVGVTDIY 20 HP SKHDSQHKLSEVITGDLLIIMAQIIVAIQMVLEEKFVYKHNVHPLRAVGTEGLFGFVILS CE YDDDPLDDKNAIITGNLLIVMAQIIVAIQMVYEQKYLTKYDVPALFAVGLEGLFGMVTLS HP LLLVPMYYIPAG-SFSGNPRGTLEDALDAFCQVGQQPLIAVALLGNISSIAFFNFAGISV 25 CE ILMIPFYYIHVPRTFSTNPEGRLEDVFYAWKEITEEPTIALALSGTVVSIAFFNFAGVSV HP TKELSATTRMVLDSLRTVVIWALSLALGWEAFHALQILGFLILLIGTALYNGLHRPLLGR ********************** CE TKELSATTRMVLDSVRTLVIWVVSIPLFHEKFIAIQLSGFAMLILGTLIYNDILIGPWFR HP LSRGRPLAEESEQERLLGGTRTPINDAS 30 CE RNILPNLSSHANCARCWLCICGGDSELIEYEQEDQEHLMEA

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. N50907) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10488> (SEQ ID Nos. 67, 77, and 87)

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Determination of the whole base sequence of the cDNA insert of clone HP10488 obtained from cDNA library of human liver revealed the structure consisting of a 39-bp untranslated region, а 273-bp ORF, and a 421-bp untranslated region. The ORF codes for a protein consisting of 90 amino acid residues and there existed one putative transmembrane domain at the N-terminus. Figure 27 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 10,151 predicted from the ORF. When expressed in COS7 cells, an expression product of about 6 observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H73534) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10538> (SEQ ID Nos. 68, 78, and 88)

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Determination of the whole base sequence of the cDNA insert of clone HP10538 obtained from cDNA library of human osteosarcoma cell Saos-2 revealed the line consisting of a 357-bp 5'-untranslated region, a 1500-bp ORF, and a 1911-bp 3'-untranslated region. The ORF codes for a protein consisting of 499 amino acid residues and there existed at least four putative transmembrane domains. Figure hydrophobicity/hydrophilicity profile, depicts the obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the mouse pore-forming K⁺ channel subunit (GenBank Accession No. AF056492). Table 19 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the mouse pore-forming K⁺ channel subunit (MM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 32.4% in the N-terminal region of 241 amino acid residues.

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Table 19

HP MVDRGPLLTSAIIFYLAIGAAIFEVLEEPHWKEAKKNYYTQKLHLLKEFPCLGQEGLDK ***. ** .*..** ..*.*. 5 MM MRSTTLLALLALVLLYLVSGALVFQALEQPHEQQAQKKMDHGRDQFLRDHPCVSOKSLED HP ILEVVSDAAGQG-----VAITGNQTFNNWNWPNAMIFAATVITTIGYGNVAPKTPAGRLF** .*..*.********* ***** MM FIKLLVEALGGGANPETSWTNSSNHSSAWNLGSAFFFSGTIITTIGYGNIVLHTDAGRLF HP CVFYGLFGVPLCLTWISALGKFFGGRAKR----LGQFLTKRGVSLRKAOITCTVIFIVWG 10 *.**.* *.***. .*.. .* *. *. MM CIFYALVGIPLFGMLLAGVGDRLGSSLRRGIGHIEAIFLKWHVPPGLVRSLSAVLFLLIG HP VLVHLVIPPFVFMVTEGWNYIEGLYYSFITISTIGFGDFVAGVNPSANYHALYRYFVELW MM CLLFVLTPTFVFSYMESWSKLEAIYFVIVTLTTVGFGDYVPG-DGTGQNSPAYOPLVWFW 15 HP IYLGLAWLSLFVNWKVSMFVEVHKAIKKRRRRKESFESSPHSRKALQVKGSTASKDVNI * .***... MM ILFGLAYFASVLTTIGNWLRAVSRRTRAEMGGLTAQAASWTGTVTARVTQRTGPSAPPPE

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R25184) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10542> (SEQ ID Nos. 69, 79, and 89)

Determination of the whole base sequence of the cDNA insert of clone HP10542 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 23-bp 5'-untranslated region, a 321-bp ORF, and a 426-bp 3'-

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untranslated region. The ORF codes for a protein consisting of 106 amino acid residues and there existed one putative transmembrane domain. Figure 29 depicts hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,724 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kpa was observed in the membrane fraction.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA029683) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10571> (SEQ ID Nos. 70, 80, and 90)

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20 Determination of the whole base sequence of the cDNA insert of clone HP10571 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 95-bp 5'-untranslated region, a 459-bp ORF, and a 675-bp 3'untranslated region. The ORF codes for a protein consisting 25 of 152 amino acid residues and there existed one putative transmembrane domain. Figure 30 depicts hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, of the present protein. translation resulted in formation of a translation product 30 of 20 kDa that was larger than the molecular weight of 17,062 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 23 kDa

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which is considered to have a sugar chain being attached after secretion. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Ile-Thr at position 10).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA105822) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP01470> (SEQ ID Nos. 91, 101, and 111)

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Determination of the whole base sequence of the cDNA insert of clone HP01470 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 157-bp 5'-untranslated region, a 1077-bp ORF, and a 385-bp 3'untranslated region. The ORF codes for a protein consisting of 358 amino acid residues and there existed one putative transmembrane domain. Figure 31 depicts hydrophobicity/hydrophilicity profile, obtained by the Kytemethod. of the present protein. translation resulted in formation of a translation product of 43 kDa that was somewhat larger than the molecular weight of 40,489 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 40 kDa from which the secretory signal is considered to have been cleaved and a product of 43.5 kDa which is considered to have been subjected to some modification. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 23. When

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expressed in COS7 cells, an expression product of about 44 kDa was observed in the supernatant fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis hypothetical protein 39.9 kDa (SWISS-PROT Accession No. Q10005). Table 20 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein 39.9 kDa (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 58.9% in the entire region.

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Table 20

HP MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALOLHPDRNPDD *.. * ********* ... * ... ******* . ***** 5 CE MRILNVSLLVLASSLVAFVECGRDFYKILGVAKNANANQIKKAYRKLAKELHPDRNODD HP PQAQEKFQDLGAAYEVLSDSEKRKQYDTYGEEGL--KDGHQSSHGDIFSHFFGDFGFMFG CE EMANEKFODLSSAYEVLSDKEKRAMYDRHGEEGVAKMGGGGGGGHDPFSSFFGDF-FG-G HP GTPRQQDRNIPRGSDIIVDLEVTLEEVYAGNFVEVVRNKPVARQAPGKRKCNCROEMRTT 10 CE GGGHGGEEGTPKGADVTIDLFVTLEEVYNGHFVEIKRKKAVYKQTSGTROCNCRHEMRTE HP QLGPGRFQMTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMEYPFIGEGEPHVDGEPGD CE QMGQGRFOMFOVKVCDECPNVKLVOENKVLEVEVEVGADNGHQQIFHGEGEPHIEGDPGD 15 HP LRFRIKVVKHPIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAK *.*.*. *** ***.******** ..* ****.* **** *.. ***.*. CE LKFKIRIOKHPRFERKGDDLYTNVTISLQDALNGFEMEIQHLDGHIVKVQRDKVTWPGAR HP LWKKGEGLPNFDNNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVO-KVYNGLOG *.**.**.*.....** ** *...*****.***...*... * ...*...*...*... 20 CE LRKKDEGMPSLEDNNKKGMLVVTFDVEFPKTELSDEQKAQIIEILQONTVKPKAYNGL

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA282838) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

30 <HP002419> (SEQ ID Nos. 92, 102, and 112)

Determination of the whole base sequence of the cDNA insert of clone HP02419 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 253-bp

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5'-untranslated region, a 681-bp ORF, and a 1120-bp 3'untranslated region. The ORF codes for a protein consisting
of 226 amino acid residues and there existed four putative
transmembrane domains. Figure 32 depicts the
hydrophobicity/hydrophilicity profile, obtained by the KyteDoolittle method, of the present protein. In vitro
translation resulted in formation of a translation product
of high molecular weight.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human hypothetical protein KIAA0108 (SWISS-PROT Accession No. Q15012). Table 21 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human hypothetical protein KIAA0108 (KI). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 43.9% in the entire region.

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Table 21

MKMVAPWTRFYSNSCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPD---QY HP ****..** ************* ...** 5 KI MVSMSFKRNRSDRFYSTRCCGCCHVRTGTIILGTWYMVVNLLMAILLTVEVTHPNSMPAV HP NFSSSELGGDFEF-MDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYQIFDF KI NIOYEVIGNYYSSERMADNACVLFAVSVLMFIISSMLVYGAISYQVGWLIPFFCYRLFDF HP ALNMLVAITVLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYL 10 KI VLSCLVAISSLTYLPRIKEYLDOL-PDFPYKDDLLALDSSCLLFIVLVFFALFIIFKAYL HP ISCVWNCYRYINGRNSSDVLVYVT-SNDTTVLLPPYDDATVNGAAKEPPPPYVSA KI INCVWNCYKYINNRNVPEIAVYPAFEAPPOYVLPTY-EMAVKMPEKEPPPPYLPA 15

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA173214) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

25 <HP02631> (SEQ ID Nos. 93, 103, and 113)

Determination of the whole base sequence of the cDNA insert of clone HP02631 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 42-bp 5'-untranslated region, a 588-bp ORF, and a 750-bp 3'-untranslated region. Although the 49th amino acid residue is encoded by a stop codon, it is likely that this codon encodes selenocysteine from the molecular weight

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of the translation product and the sequence comparison data with the Caenorhabditis elegans homologue. The ORF codes for a protein consisting of 195 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the intermediate region. Figure 33 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 58 kDa. In this case, the addition of a microsome led to the formation of a product of 56 kDa from which the secretory signal is considered to have been cleaved. Since both of these products are larger than the molecular weight of 22 kDa predicted from the ORF, it is likely that the protein interacts with another protein.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Caenorhabditis hypothetical protein C35C5.3 (EMBL Accession No. Z78417). Table 22 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein C35C5.3 (CE). U at position 49 in the amino acid sequence of the protein of the present invention represents selenocysteine. Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.9% in the entire region other than the Nterminal region. Cystein was found in the sequence of the C. elegans protein at the posistion corresponding to position 49 encoded by the stop codon (selenocysteine) of the protein of the present invention.

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Table 22

HP MRLLLL 5 CE MRIHDELQKODMSRFGVFIIGVLFFMSVCDVLRTEEHSHDENHVHEKDDFEAEFGDETDS HP LLVAASAMVRSEASANLGGVPSKRLKMQYATGPLLKFQICVSUGYRRVFEEYMRVISORY *** **...*... CE QSFSQGTEEDHIEVREOSSFVKPTAVHHAKDLPTLRIFYCVSCGYKOAFDOFTTFAKEKY HP PDIRIEGENYLPOPIYRHIASFLSVFKLVLIGLIIVGKDPFAFFGMOAPSIWOWGOENKV 10 ..* ** *... *.. * .**. **. CE PNMPIEGANFAPVLWKAYVAQALSFVKMAVLVLVLGGINPFERFGLGYPQILQHAHGNKM HP YACMMVFFLSNMIENQCMSTGAFEITLNDVPVWSKLESGHLPSMQQLVQILDNEMKLNVH CE SSCMLVFMLGNLVEQSLISTGAFEVYLGNEQIWSKIESGRVPSPQEFMOLIDAOLAVLGK 15 HP MDSIPHHRS CE APVNTESFGEFQQTV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA156969) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02695> (SEQ ID Nos. 94, 104, and 114)

Determination of the whole base sequence of the cDNA insert of clone HP02695 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 112-bp 5'-untranslated region, a 1020-bp ORF, and a 160-bp 3'-

untranslated region. The ORF codes for a protein consisting of 339 amino acid residues and there existed three putative transmembrane domains. Figure 34 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 38 kDa that was almost identical with the molecular weight of 38,274 kDa predicted from the ORF.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the rat hypertension-induced protein S-2 fragment (PIR Accession No. 539959). Table 23 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the rat hypertension-induced protein S-2 fragment (RN). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 74.3% in the entire region.

Table 23

HP MNWELLLWLLVLCALLLLLVQLLRFLRADGDLTLLWAEWQGRRPEWELTDMVVWVTGASS

5 HP GIGEELAYQLSKLGVSLVLSARRVHELERVKRRCLENGNLKEKDILVLPLDLTDTGSHEA

RN VKRRSLENGNLKEKDILVLPLDLADTSSHDI

RN ATKTVLQEFGRIDILVNNGGVAHASLVENTNMDIFKVLIEVNYLGTVSLTKCFLPHMMER

HP KQGKIVTVNSILGIISVPLSIGYCASKHALRGFFNGLRTELATYPGIIVSNICPGPVQSN .*****...*

RN NQGKIVVMKS

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. T84331) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10031> (SEQ ID Nos. 95, 105, and 115)

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Determination of the whole base sequence of the cDNA insert of clone HP10031 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 55-bp 5'-untranslated region, a 1464-bp ORF, and a 649-bp 3'-untranslated region. The ORF codes for a protein consisting of 487 amino acid residues and there existed eleven putative transmembrane domains. Figure 35 depicts the hydrophobicity/hydrophilicity profile, obtained

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by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. When expressed in COS7 cells, an expression product of about 55 kDa was observed in the membrane fraction.

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The search of the protein data base using the amino acid sequence of the present protein revealed that the the Caenorhabditis elegans similar protein was to CELK07H8 (GenBank Accession hypothetical protein AF047659). Table 24 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein CELK07H8 Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 44.2% in the entire region.

Table 24

HP MDGTETRQRRLDSCGKPGELGLPHPLSTGGLPVAS 5 CE MKGGGGIGDGKKDYQSAVHEGLTTFDQLGIALEDVGKSMDAETATPGGSLFSRVIFRFRN HP EDGALRAPESQSVTPKPLETEPSRETAWSIGLQVTVPFMFAGLGLSWAGMLLDYFQHWPV . . *... . . ** ** **** . . ** . . *. CE ENSSLKSRTYDHSNDLVNMSVIPAESSYVLFFQVLFPFAVAGLGMVFAGLVLSIVVTWPL HP FVEVKDLLTLVPPLVGLKGNLEMTLASRLSTAANTGQIDDPQEQHRVISSNLALIQVQAT 10 * *. ..*.**.*.********** ** *..*.... *. .**** CE FEEIPEILILVPALLGLKGNLEMTLASRLSTLANLGHMDSSKQRKDVVIANLALVQVQAT HP VVGLLAAVAALLLGVVSREEVDVAKVELLCASSVLTAFLAAFALGVLMVCIVIGARKLGV CE VVAFLASAFAAALAFIPSGDFDWAHGALMCASSLATACSASLVLSLLMVVVIVTSRKYNI 15 HP NPDNIATPIAASLGDLITLSILALVSSFFYR-HKDSRYLTPLVCLSFAALTPVWVLIAKO ****.*************************** CE NPDNVATPIAASLGDLTTLTVLAFFGSVFLKAHNTESWLNVIVIVLFLLLLPFWIKIANE HP SPPIVKILKFGWFPIILAMVISSFGGLILSKTVSKQQYKGMAIFTPVICGVGGNLVAIQT . . . * ** * . * . * . * * * * . . . * * * * * * * * * . 20 CE NEGTQETLYNGWTPVIMSMLISSAGGFILETAV--RRYHSLSTYGPVLNGVGGNLAAVQA HP SRISTYLHMWSAPGVLPLQ--MKKFWPNPCSTFCTSEINSMSARVLLLLVVPGHLIF-FY CE SRLSTYFHKAGTVGVLPNEWTVSRF-TSVQRAFFSKEWDSRSARVLLLLVVPGHICFNFL HP I-IYLVEGQSVINSQ--TFVVLYLLAGLIQVTILLYLAEVMVRLTWHQALDPDNHCIPYL 25 *. **..*..****.. ...* * *. ...** *** CE IQLFTLTSKNNVTPHGPLFTSLYMIAAIIQVVILLFVCQLLVALLWKWKIDPDNSVIPYL HP TGLGDLLGTGLLALCFFTDWLLKSKAELGGISELASGPP *.****** CE TALGOLLGTGLLFIVFLTTDHFDPKELTSS 30

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

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example, Accession No. AA334000) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP10530> (SEQ ID Nos. 96, 106, and 116)

Determination of the whole base sequence of the cDNA insert of clone HP10530 obtained from cDNA library of human cell line Saos-2 revealed the structure consisting of a 80-bp 5'-untranslated region, a 1182-bp ORF, and a 95-bp 3'-untranslated region. The ORF codes for a protein consisting of 393 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 36 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 46 kDa that was somewhat larger than the molecular weight of 44,912 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 45.5 kDa from which the secretory signal is considered to have been cleaved. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 23. When expressed in COS7 cells, an expression product of about 43 kDa was observed in the supernatant fraction and the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Arabidopsis thaliana hypothetical protein IG002N01 (GenBank Accession No. AF007269). Table 25 shows the comparison between amino acid sequences of the

human protein of the present invention (HP) and the A. thaliana hypothetical protein IG002N01 (AT). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 27.0% in the N-terminal region of 355 amino acid residues.

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Table 25

HP MRTLFNLLWL 5 AT MELTSFQKSPSSNDVVSFSVSLVRNSMARRRRSSAAESLKRRNDGYESLCQVVOODSDRR HP ALACSPVHTTLSKSDAKKAASKTLLEKSQFSDKPVQDRGLVVTDLKAESVVLEHRSYCSA*.* **.. **.. AT LITIFVIFFIVIPAVSIAVYKVKFADRVIQTESSIRQKGIVKTDINFQEILTEHSK--AS HP KARDRHFAGDVLGYVTPWNSHGYDVTKVFGSKFTQISPVWLQ-LKRRGREMFEVTGLHDV 10 AT ENSTRHYDYPVLAYITP--CQGSGL--VLEGR-HNADKGWIQELRSRGNALSASKGLPKL HP DQGWMRAVRKHAKGLHIVPRLLFEDWTYDDFRNVLDSEDEIEELSKTVVQVAKNQHFDGF AT ---YNSCIFHALKRMNFFTLELVNFNTYLVIMFALNS-REMEYNGIVLESWSRWAAYGVL 15 HP VVEVWNQLLSQKRVGLIHMLTHLAEALHQARLLALLVIPPAITPGTDQLGMFTHKEFEOL * . * * . *.... * AT HDPDLRKMALKFVKOLGDALHSTSSPRNNQQHMQFMYVVGPPRSEKLQMYDFGPEDLOFL HP APVLDGFSLMTYDYSTAHOPGPNAPLSWVRACVQ-VLDPKSK----WRSKILLGLNFYGM .********.*.... 20 AT KDSVDGFSLMTYDFSNPQNPGPNAPVKWIDLTLKLLLGSSNNIDSNIARKVLLGINFYGN HP DYATSKDAREPVVGARYIOTLKDHRPRMVWDSQASEHFFEYKKSRSGRHVVFYPTLKSLO AT DFVISGGGGGAITGRDYLALLOKHKPTFRWDKESGEHLFMYRDDKNIKHAVFYPTLMSIL HP VRLELARELGVGVSIWELGQGLDYFYDLL 25 .*** ** *.*.***.**. ..* AT LRLENARLWGIGISIWEIGQDKGHFGKYAEASLEASSIFSGHTFDMQFRTNPRQLSRNGS

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA302913) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the

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protein of the present invention.

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<HP10541> (SEQ ID Nos. 97, 107, and 117)

Determination of the whole base sequence of the cDNA insert of clone HP10541 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 7-bp 5'-untranslated region, a 591-bp ORF, and a 113-bp 3'untranslated region. The ORF codes for a protein consisting of 196 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 37 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kytemethod, protein. of the present Doolittle translation resulted in formation of a translation product of 23 kDa that was somewhat larger than the molecular weight of 21,553 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of 20 kDa from which the secretory signal is considered to have been cleaved and a product of 23 kDa which is considered to have a sugar chain being attached. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from glycine at position 41. In addition, there exists in the amino acid sequence of this protein one site at which N-glycosylation may occur (Asn-Leu-Thr at position 185).

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human zymogen membrane protein (GenBank Accession No. AF056492). Table 26 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human zymogen membrane protein (ZM). Therein, the marks of -, *, and . represent a

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gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 37.6% in the C-terminal region of 133 amino acid residues.

Table 26

HP MWRVPGTTRRPVTGESPGMHRPEAMLLLLTLALLGGPTWAGKMYGPGGGKYFS-TTEDYD 10 **.*** ** . . . * ZM MLTVALLALLCASASGNAIQARSSSYSGEYGSGGGKRFSHSGNOLD HP HEITGLRVSVGLLLVKSVQVKLGDSWDVKLGALGGNTQEVTLQPGEYITKVFVAFQAFLR . ..**. *. *. .*. .*. *. *.** ZM GPITALRVRVNTYYIVGLQVRYGKVWSDYVGGRNGDLEEIFLHPGESVIQVSGKYKWYLK 15 HP GMVMYTSKDRYFYFGKLDGOISSAYPSOEGOVLVGIYGQYQLLGIKSIGFEWN-YPLEEP .*. *.*.**. *** .* .* * . . ** * *. ZM KLVFVTDKGRYLSFGKDSGTSFNAVPLHPNTVLRFISGRSGSL-IDAIGLHWDVYPTSCS HP TTEPPVNLTYSANSPVGR 20 ZM RC

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA340605) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10550> (SEQ ID Nos. 98, 108, and 118)

Determination of the whole base sequence of the cDNA

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insert of clone HP10550 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 241-bp 5'-untranslated region, a 324-bp ORF, and a 86-bp untranslated region. The ORF codes for a protein consisting of 107 amino acid residues and there existed one putative 38 transmembrane domain. Figure depicts hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA348310) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10590> (SEQ ID Nos. 99, 109, and 119)

Determination of the whole base sequence of the cDNA insert of clone HP10590 obtained from cDNA library of human line HT-1080 revealed the structure fibrosarcoma cell consisting of a 77-bp 5'-untranslated region, a 1053-bp ORF, and a 180-bp 3'-untranslated region. The ORF codes for a protein consisting of 350 amino acid residues and there existed one putative transmembrane domain. Figure 39 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 40 kDa that was almost identical with the molecular weight of 39,285 predicted from the ORF. In this case, the addition of a microsome led to the formation of a product of

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43 kDa which is considered to have a sugar chain being attached. In addition, there exist in the amino acid sequence of this protein two sites at which N-glycosylation may occur (Asn-Asn-Ser at position 144 and Asn-Leu-Thr at position 328).

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA461346) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10591> (SEQ ID Nos. 100, 110, and 120)

Determination of the whole base sequence of the cDNA insert of clone HP10591 obtained from cDNA library of human fibrosarcoma cell line HT-1080 revealed the structure consisting of a 232-bp 5'-untranslated region, a 324-bp ORF, and a 844-bp 3'-untranslated region. The ORF codes for a protein consisting of 107 amino acid residues and there existed one putative transmembrane domain. Figure 40 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 11,328 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H09424) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein

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of the present invention.

<HP01462> (SEQ ID Nos. 121, 131, and 141)

Determination of the whole base sequence of the cDNA insert of clone HP01462 obtained from cDNA library of human cell line HT-1080 revealed the structure fibrosarcoma consisting of a 121-bp 5'-untranslated region, a 1452-bp ORF, and a 477-bp 3'-untranslated region. The ORF codes for a protein consisting of 483 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 41 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 72 kDa that was larger than the molecular weight 55,838 predicted from the of Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from lysine at position 21.

The search of the protein data base using the amino acid sequence of the present protein revealed that the the Caenorhabditis similar to was hypothetical protein ZK1058.4 (EMBL Accession No. Z35604). Table 27 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein ZK1058.4 (CE). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both shared a homology of 35.6% in the entire region.

Table 27

HP MKAFHTFCVVLLVFGSVSEAKFDDFEDEEDIVEYDDNDFAEFEDVMEDSVTESPQRVIIT 5 CE MKIVWIFLIFFIGFAIST HP EDDE-DETTVELEGQDENQEGDFEDADTQEGDTESEPYDDEEFEGYEDKP-----D .*.* .* . *. * ...*.*.*. *..* CE DDNEFAEFEDEFVGSSATQAPEIQREGEPPVLKQKDDFEEEDFGVVEEEPEEAEKVREAD HP TSSSKNKDPITIVDVPAHLQNSWESYYLEILMVTGLLAYIMNYIIGKNKNSRLAQAWFNT 10 .*...*****...* CE SDDAAPAOPLKFADVPAHFRSNWASYQVEGIVVLIILIYMTNYLIGKTTNASIAQTIFDM HP HRELLESNFTLVGDDGTNKEATSTGKLNQENEHIYNLWCSGRVCCEGMLIQLRFLKRQDL CE CRPTLEEOFAVVGDDGTTDLDKMIPSLKHDTDSTFSAWCTGRVNVNSLFLOMKMVKRODV 15 HP LNVLARMMRPVSDOVOIKVTMN-DEDMDTYVFAVGTRKALVRLQKEMQDLSEFCSDKPKS CE VSRIMEMFTPSGDKMTIKASLETTNDTDPLIFAVGEKKIASKYFKEMLDLNSFASERKOA HP GAKYGLPDSLAILSEMGEVTDGMMDTKMVHFLTHYADKIESVHFSDQFSGPKIMQEEGQP 20 CE AOOFNLPASWOVYADONEVVFSILDPGVVSLLKKHEDAIEFIHISDQFTGPKPAEGESYT HP LKLPDTKRTLLFTFNVPGSGNTYPKDMEALLPLMNMVIYSIDKAKKFRLNREGKQKADKN .**...**.. * .* *... ..*.* ****.*..* ***... CE -RLPEAQRYMFVSLNLQYLG----QDEESVMEILNLVFYLIDKARKMKLSKDAKVKAERR HP RARVEENFLKLTHVQRQEAAQSRREEKKRAEKERIMNEEDPEKQRRLEEAALRREQKKLE 25 CE RKEFEDAFLKOTHOFROEAAOARREEKTRERKOKLMDESDPEROKRLEAKELKREAKA--HP KKQMKMKQIKVKAM * ****.** CE -KSPKMKOLKVK 30

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for

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example, Accession No. AA307793) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

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<HP02485> (SEQ ID Nos. 122, 132, and 142)

Determination of the whole base sequence of the cDNA insert of clone HP02485 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 69-bp 5'-untranslated region, a 1005-bp ORF, and a 1672-bp 3'untranslated region. The ORF codes for a protein consisting of 334 amino acid residues and there existed one putative 42 depicts domain. Figure transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, the present protein. of translation resulted in formation of a translation product of 36 kDa that was almost identical with the molecular weight of 38,171 predicted from the ORF. When expressed in COS7 cells, an expression product of about 23 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that similar the Caenorhabditis was to hypothetical protein W01A11.2 (GenBank Accession No. U64852). Table 28 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein W01A11.2 (CE). marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 45.5% in the entire region.

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Table 28

MVEFAPLFMPWERRLQTLAVLQFVFSFLALAEICT-V HP .***..**.***** *.* .. *. 5 CE MRLRLSSISGKAKLPDKEICSSVSRILAPLLVPWKRRLETLAVMGFIFMWVILPIMDLWV HP GFIALLFTRFWLLTVLYAAWWYLDRDKPRQGGRHIQAIRCWTIWKYMKDYFPISLVKTAE CE PFHVLFNTRWWFLVPLYAVWFYYDFDTPKKASRRWNWARRHVAWKYFASYFPLRLIKTAD HP LDPSRNYIAGFHPHGVLAVGAFANLCTESTGFSSIFPGIRPHLMMLTLWFRAPFFRDYIM 10 CE LPADRNYIIGSHPHGMFSVGGFTAMSTNATGFEDKFPGIKSHIMTLNGQFYFPFRREFGI HP SAGLVTSEKESAAHILNRKGGGNLLGIIVGGAQEALDARPGSFTLLLRNRKGFVRLALTH * .. .*** ...*. * *. .*.** ***.*.*. ** * **.** . **. 15 CE MLGGIEVSKESLEYTLTKCGKGRACAIVIGGASEALEAHPNKNTLTLINRRGFCKYALKF HP GAPLVPIFSFGENDLFDQIPNSSGSWLRYIQNRLQKIMGISLPLFHGRGVF-QYSFGLIP CE GADLVPMYNFGENDLYEQYENPKGSRLREVQEKIKDMFGLCPPLLRGRSLFNQYLIGLLP HP YRRPITTVVGKPIEVOKTLHPSEEEVNQLHQRYIKELCNLFEAHKLKFNIPADQHLEFC 20 CE FRKPVTTVMGRPIRVTOTDEPTVEOIDELHAKYCDALYNLFEEYKHLHSIPPDTHLIFQ

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D25664) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP02798> (SEQ ID Nos. 123, 133, and 143)

Determination of the whole base sequence of the cDNA

insert of clone HP02798 obtained from cDNA library of human line HT-1080 revealed the fibrosarcoma cell consisting of a 31-bp 5'-untranslated region, a 804-bp ORF, and a 301-bp 3'-untranslated region. The ORF codes for a protein consisting of 267 amino acid residues and there existed four putative transmembrane domains. depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 29 kDa that was almost identical with the molecular weight of 30,778 predicted from the ORF. When expressed in COS7 cells, an expression product of about 26 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the human DHHC-containing cysteinerich protein (GenBank Accession No. U90653). Table 29 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human DHHCcontaining cysteine-rich protein (DH). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 35.0% in the intermediate region of 100 amino The positions of seven cysteines acid residues. conserved between the two proteins. The protein of the present invention also had the DHHC (Asp-His-His-Cys) sequence.

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Table 29

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. D79050) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10041> (SEQ ID Nos. 124, 134, and 144)

Determination of the whole base sequence of the cDNA insert of clone HP10041 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 12-bp 5'-untranslated region, a 321-bp ORF, and a 286-bp 3'-untranslated region. The ORF codes for a protein consisting of 106 amino acid residues and there existed one putative transmembrane domain. Figure 44 depicts

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the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 12 kDa that was almost identical with the molecular weight of 12,060 predicted from the ORF. When expressed in COS7 cells, an expression product of about 13 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the the Caenorhabditis similar to protein was hypothetical protein K10B2.4 (GenBank Accession No. U28730). Table 30 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the C. elegans hypothetical protein K10B2.4 (CE). Therein, marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The both proteins shared a homology of 62.1% in the entire region.

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Table 30

HP MSTNNMSDPRRPNKVLRYKP---PPSECNPALDDPTPDYMNLLGMIFSMCGLMLKLKWCA

CE MQQNGDPRRTNRIVRYKPLDSTANQQQAISEDPLPEYMNVLGMIFSMCGLMIRMKWCS

HP WVAVYCSFISFANSRSSEDTKQMMSSFMLSISAVVMSYLQNPQPMTPPW

.. ** *****.*.*.*.***********

CE WLALVCSCISFANTRTSDDAKQIVSSFMLSVSAVVMSYLQNPSPIIPPWVTLLQS

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Furthermore, the search of the GenBank using the base

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sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H20098) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10246> (SEQ ID Nos. 125, 135, and 145)

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Determination of the whole base sequence of the cDNA insert of clone HP10246 obtained from cDNA library of human epidermoid carcinoma cell line KB revealed the structure consisting of a 110-bp 5'-untranslated region, a 675-bp ORF, and a 79-bp 3'-untranslated region. The ORF codes for a protein consisting of 224 amino acid residues and there existed five putative transmembrane domains. Figure 45 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 23 kDa that was somewhat smaller than the molecular weight of 25,244 predicted from the ORF. When expressed in COS7 cells, an expression product of about 21 kDa was observed in the membrane fraction.

The search of the protein data base using the amino acid sequence of the present protein revealed that the similar the putative protein was to human seven transmembrane domain protein (GenBank Accession No. Y18007). Table 31 shows the comparison between amino acid sequences of the human protein of the present invention (HP) and the human putative seven transmembrane domain protein (TM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that

of the protein of the present invention, respectively. The both proteins shared a homology of 93.3% in the entire region.

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Table 31

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Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA453931) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10392> (SEQ ID Nos. 126, 136, and 146)

TM FVMETFVHLCSLGSWAVLMAGVVVKGLLVIRNLAMYVAVVNVHS

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Determination of the whole base sequence of the cDNA insert of clone HP10392 obtained from cDNA library of human osteosarcoma cell line U-2 OS revealed the structure

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consisting of a 24-bp 5'-untranslated region, a 777-bp ORF, and a 726-bp 3'-untranslated region. The ORF codes for a protein consisting of 258 amino acid residues and there existed a putative secretory signal at the N-terminus. Figure 46 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 34 kDa that was somewhat larger than the molecular weight of 29,623 predicted from the ORF. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from leucine at position 49.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. H15999) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention. In addition, partial identity with the hypothetical protein KIAA0384 (Accession No. AB002382) was observed, although the hypothetical protein had a different ORF.

<HP10489> (SEQ ID Nos. 127, 137, and 147)

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Determination of the whole base sequence of the cDNA insert of clone HP10489 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 137-bp 5'-untranslated region, a 333-bp ORF, and a 189-bp 3'-untranslated region. The ORF codes for a protein consisting of 110 amino acid residues and there existed two putative transmembrane domains. Figure 47 depicts the

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hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of 19 kDa that was somewhat larger than the molecular weight of 12,010 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA262162) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10519> (SEQ ID Nos. 128, 138, and 148)

Determination of the whole base sequence of the cDNA insert of clone HP10519 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 67-bp 5'-untranslated region, a 276-bp ORF, and a 367-bp 3'untranslated region. The ORF codes for a protein consisting of 91 amino acid residues and there existed one putative domain. Figure 48 depicts transmembrane hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. translation resulted in formation of a translation product of 10 kDa that was almost identical with the molecular weight of 10,275 predicted from the ORF.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. W16639) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein

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of the present invention.

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<HP10531> (SEQ ID Nos. 129, 139, and 149)

Determination of the whole base sequence of the cDNA insert of clone HP10531 obtained from cDNA library of human osteosarcoma cell line Saos-2 revealed the structure consisting of a 55-bp 5'-untranslated region, a 1035-bp ORF, and a 1092-bp 3'-untranslated region. The ORF codes for a protein consisting of 344 amino acid residues and there existed five putative transmembrane domains. Figure 49 depicts the hydrophobicity/hydrophilicity profile, obtained by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight.

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. R50695) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

<HP10574> (SEQ ID Nos. 130, 140, and 150)

Determination of the whole base sequence of the cDNA insert of clone HP10574 obtained from cDNA library of human stomach cancer revealed the structure consisting of a 210-bp 5'-untranslated region, a 1287-bp ORF, and a 1276-bp 3'-untranslated region. The ORF codes for a protein consisting of 428 amino acid residues and there existed a putative secretory signal at the N-terminus and one putative transmembrane domain in the intermediate region. Figure 50 depicts the hydrophobicity/hydrophilicity profile, obtained

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by the Kyte-Doolittle method, of the present protein. In vitro translation resulted in formation of a translation product of high molecular weight. Application of the (-3,-1) rule, a method for predicting the cleavage site of the secretory signal sequence, allows to expect that the mature protein starts from serine at position 36.

The search of the protein data base using the amino acid sequence of the present protein revealed that the protein was similar to the Drosophila melanogaster GOLIATH protein (SWISS-PROT Accession No. Q06003). Table 32 shows the comparison between amino acid sequences of the human of protein present invention (HP) the and the melanogaster GOLIATH protein (DM). Therein, the marks of -, *, and . represent a gap, an amino acid residue identical with that of the protein of the present invention, and an amino acid residue similar to that of the protein of the present invention, respectively. The intermediate region of 169 amino acids of the protein of the present invention shared a homology of 41.4% with the N-terminal region of the D. melanogaster GOLIATH protein.

Table 32

HP MGPPPGAGVSCRGGCGFSRLLAWCFLLALSPQAPGSRGAEAVWTAYLNVSWRVPHTGVNR HP TVWELSEEGVYGQDSPLEPVAGVLVPPDGPGALNACNPHTNFTVPTVWGSTVOVSWLALT 5 HP QRGGGCTFADKIHLAYERGASGAVIFNFPGTRNEVIPMSHPGAVDIVAIMIGNLKGTKIL .*.*... * .. DM **MQLEKMQIKGKTRNIAAVITYQNIGQDLS** HP QSIQRGIQVTMVIEVGKK---HGPWVNHYSIFFVSVSFFIITAATVGYFIFYSARRLRNA . .*. *..***.* **.*** .*.* 10 DM LTLDKGYNVTISIIEGRRGVRTISSLNRTSVLFVSIS-FIV-DDILCWLIFYYIQRFRYM HP RAQSRKQRQLKADAKKAIGRLQLRTLKQGDKEIGPDGDSCAVCIELYKPNDLVRILTCNH DM QAKDQQSRNLCSVTKKAIMKIPTKTGKFSD-EKDLDSDCCAICIEAYKPTDTIRILPCKH HP IFHKTCVDPWLLEHRTCPMCKCDILKALGIEVDVEDGSVSLQVPVSNEISNSASSHEEDN 15 ***.*.******** * * * * * DM EFHKNCIDPWLIEHRTCPMCKLDVLKFYGYVVGDQIYQTPSPQHTAPIASIEEVPVIVVA HP RSETASSGYASVQGTDEPPLEEHVQSTNESLQLVNHEANSVAVDVIPHVDNPTFEEDETP DM VPHGPQPLQPLQASNMSSFAPSHYFQSSRSPSSSVQQQLAPLTYQPHPQQAASERGRRNS 20 HP NQETAVREIKS DM APATMPHAITASHOVTDV

Furthermore, the search of the GenBank using the base sequences of the present cDNA has revealed the registration of sequences that shared a homology of 90% or more (for example, Accession No. AA155685) in ESTs, but, since they are partial sequences, it can not be judged whether or not any of these sequences codes for the same protein as the protein of the present invention.

INDUSTRIAL APPLICABILITY

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The present invention provides human proteins having hydrophobic domains, DNAs coding for these proteins, expression vectors for these DNAs as well as eucaryotic cells expressing these DNAs. All of the proteins of the present invention are secreted or exist in the cell membrane, so that they are considered to be proteins controlling the proliferation and/or the differentiation of Accordingly, the proteins of the present invention can be employed as pharmaceuticals such as carcinostatic agents control the proliferation which act to and/or the differentiation of the cells, or as antigens for preparing antibodies against these proteins. The DNAs of the present utilized as probes for invention can be the diagnosis and gene sources for the gene therapy. Furthermore, the DNAs can be utilized for large-scale expression of these proteins. Cells into which these genes are introduced to express these proteins, can be utilized for detection of the corresponding receptors and ligands, screening of novel lowmolecular pharmaceuticals, and so on.

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The present invention also provides genes corresponding polynucleotide sequences disclosed to "Corresponding genes" are the regions of the genome that are from transcribed to produce the mRNAs which CDNA and derived polynucleotide sequences are may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with using the sequence information disclosed known methods Such methods include the preparation of probes or herein.

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primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

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Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and 1994. Trends Pharmacol. Sci. 15(7): 250-254: Lavarosky et al., 1997, Biochem. Mol. Med. 62(1): 11-22; and Hampel, 1998, Prog. Nucleic Acid Res. Mol. Biol. 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 Bl, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished

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through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, Bioessays 14(9): 629-633; Zwaal et al., 1993, Proc. Natl. Acad. Sci. USA 90(16): 7431-7435; Clark et al., 1994, Proc. Natl. Acad. Sci. 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour et al., 1988, Nature 336: 348-352; U.S. 5,464,764; 5,487,992; Patent Nos. 5,627,059; 5,631,153; 396; 5,616,491; and 5,679,523; all of which are 5,614, incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s). Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more

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preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

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homologs of the disclosed polynucleotides Species and proteins are also provided by the present invention. As "species homologue" is а herein, а protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides

capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table 33 below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

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Table 33

Stringency	Polynucleotide	Hybrid	Hybridization Temperature	Wash
Condition	Hybrid	Length	and Buffer [†]	Temperature
		(bp) [‡]		and Buffer [†]
A	DNA: DNA	≥50	65°C; 1×SSC -or-	65°C; 0.3×SSC
			42°C; 1×SSC,50% formamide	
В	DNA : DNA	< 50	T _B *; 1×SSC	T _B *; 1×SSC
C	DNA: RNA	≥50	67°C; 1×SSC -or-	67°C; 0.3×SSC
			45°C; 1×SSC,50% formamide	
D	DNA: RNA	< 50	T _D *; 1×SSC	T _D *; 1×SSC
E	RNA: RNA	≥50	70°C; 1×SSC -or-	70°C; 0.3×SSC
			50°C; 1×SSC,50% formamide	
F	RNA: RNA	<50	T _F *; 1×SSC	T _F *; 1×SSC
G	DNA : DNA	≥50	65°C; 4×SSC -or-	65°C; 1×SSC
			42°C; 4×SSC,50% formamide	
Н	DNA : DNA	<50	T _H *; 4×SSC	T _H *; 4×SSC
I	DNA: RNA	≥50	67°C; 4×SSC -or-	67°C; 1×SSC
			45°C; 4×SSC,50% formamide	1
J	DNA: RNA	<50	T _J *; 4×SSC	T _J *; 4×SSC
K	RNA: RNA	≥50	70°C; 4×SSC -or-	67℃; 1×SSC
			50°C; 4×SSC,50% formamide	
L	RNA: RNA	<50	T _L *; 2×SSC	T _L *; 2×SSC
M	DNA : DNA	≥50	50°C; 4×SSC -or-	50°C; 2×SSC
			40°C; 6×SSC,50% formamide	
N	DNA : DNA	<50	T _N *; 6×SSC	T _N *; 6×SSC
0	DNA: RNA	≥50	55°C; 4×SSC -or-	55°C; 2×SSC
			42°C; 6×SSC,50% formamide	
P	DNA: RNA	<50	T _P *; 6×SSC	T _P *; 6×SSC
Q	RNA : RNA	≥50	60°C; 4×SSC -or-	60°C; 2×SSC
	,		45°C; 6×SSC,50% formamide	
R	RNA : RNA	<50	T _R *; 4×SSC	T _R *; 4×SSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

 \dagger : SSPE (1×SSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH7.4) can be substituted for SSC (1×SSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than

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50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(^{\circ}C)=2(\#of\ A+T\ bases)+4(\#of\ G+C\ bases)$. For hybrids between 18 and 49 base pairs in length, $T_m(^{\circ}C)=81.5+16.6(\log_{10}(Na^+))+0.41$ (%G+C) - (600/N), where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1×SSC=0.165M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and Current Protocols in Molecular Biology, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

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CLAIMS

- 1. A protein comprising any one of an amino acid sequence selected from the group consisting of SEQ ID Nos. 1 to 10, 31 to 40, 61 to 70, 91 to 100, and 121 to 130.
- 2. An isolated DNA coding for the protein according to Claim 1.
- 3. An isolated cDNA comprising any one of a base sequence selected from the group consisting of SEQ ID Nos. 11 to 20, 41 to 50, 71 to 80, 101 to 110, and 131 to 140.
- 4. The cDNA according to Claim 3 consisting of any one of a base sequence selected from the group consisting of SEQ ID Nos. 21 to 30, 51 to 60, 81 to 90, 111 to 120, and 141 to 150.
- 5. An expression vector that is capable of expressing the DNA according to any one of Claim 2 to Claim 4 by in vitro translation or in eucaryotic cells.
- 6. A transformed eucaryotic cell that is capable of expressing the DNA according to any one of Claim 2 to Claim
 4 and of producing the protein according to Claim 1.

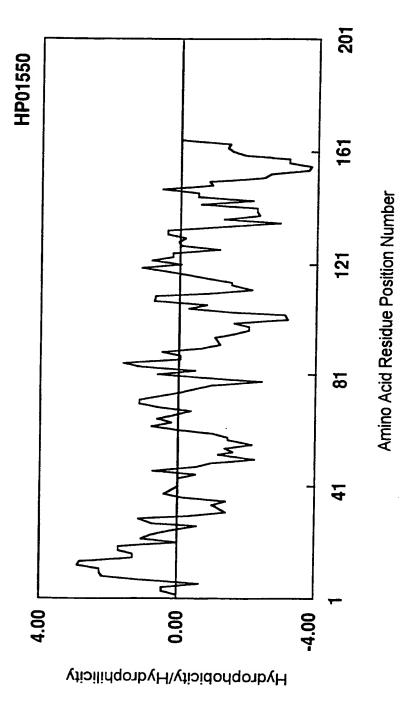


Fig. 1

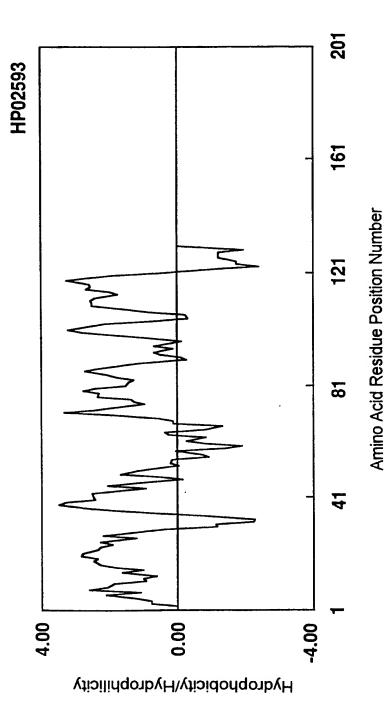


Fig. 2

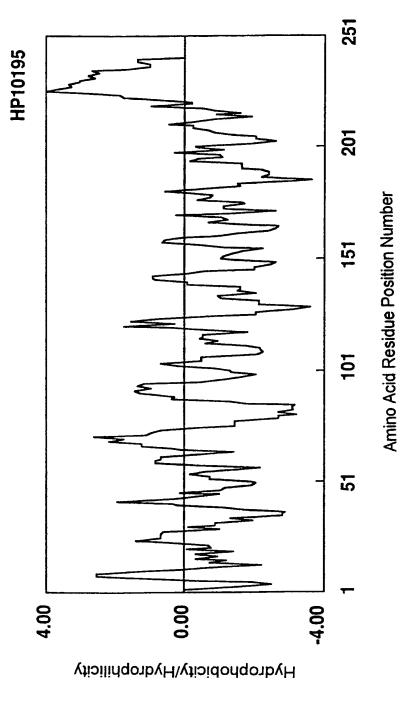


Fig. 3

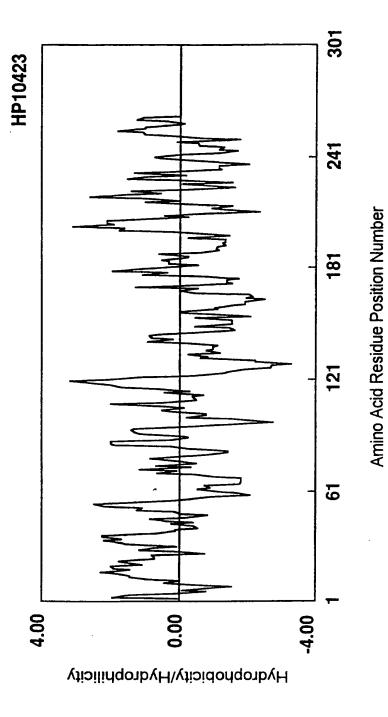


Fig 4

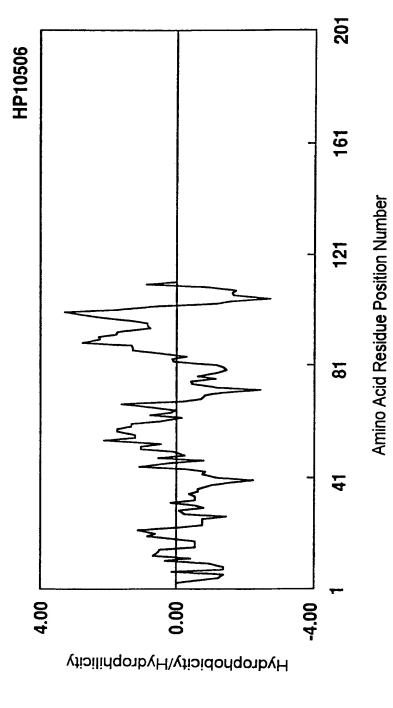


Fig. 5

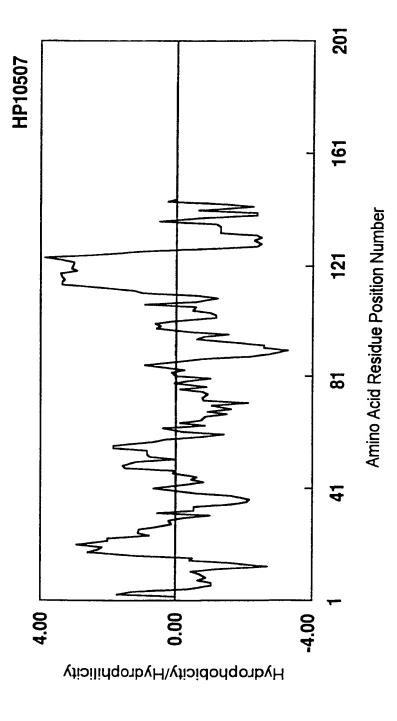


Fig. 6

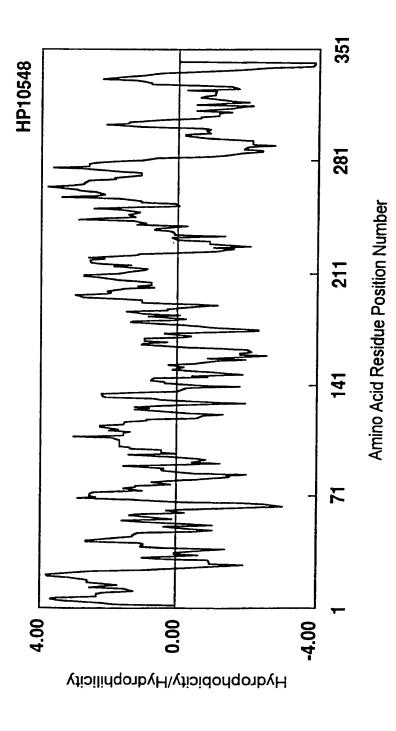
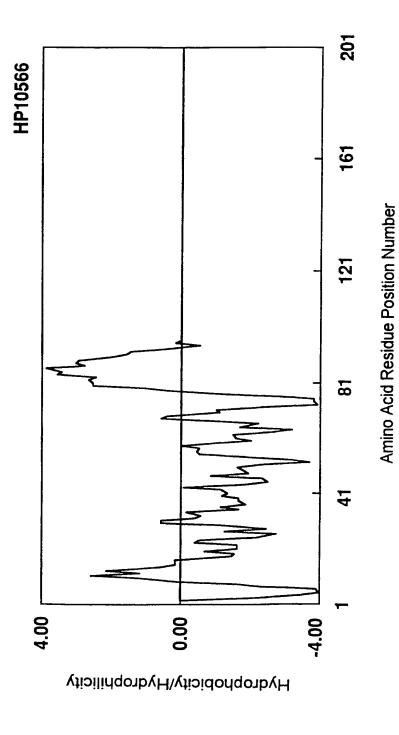


Fig. 7



α Σ

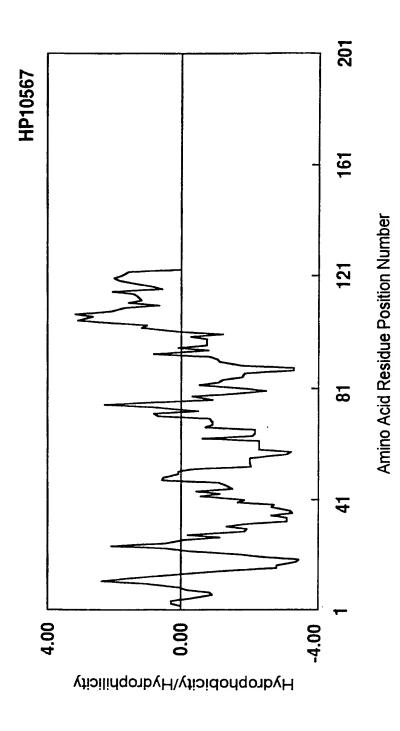


Fig. 9

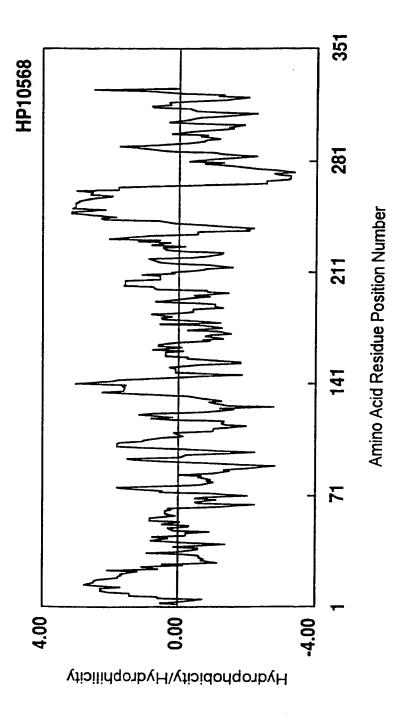


Fig. 10

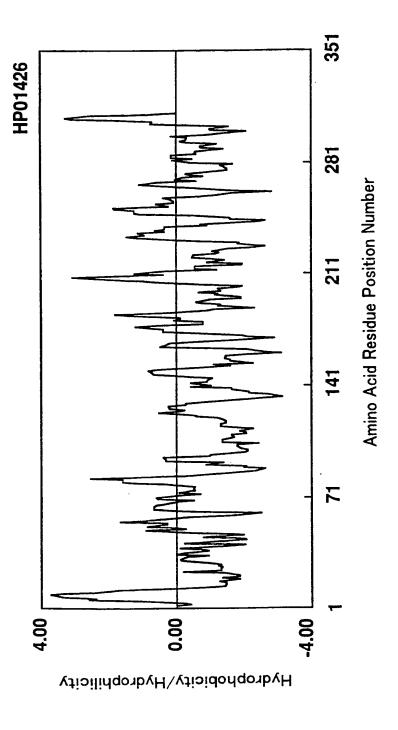


Fig. 11

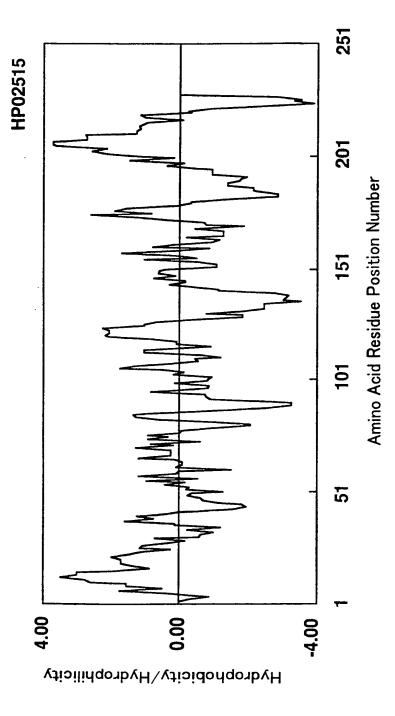


Fig. 12

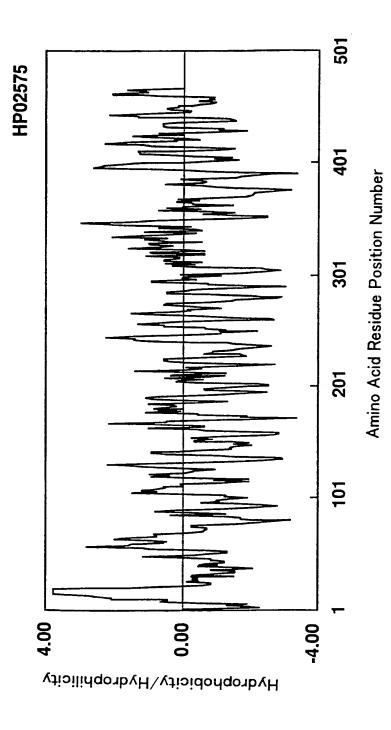


Fig. 13

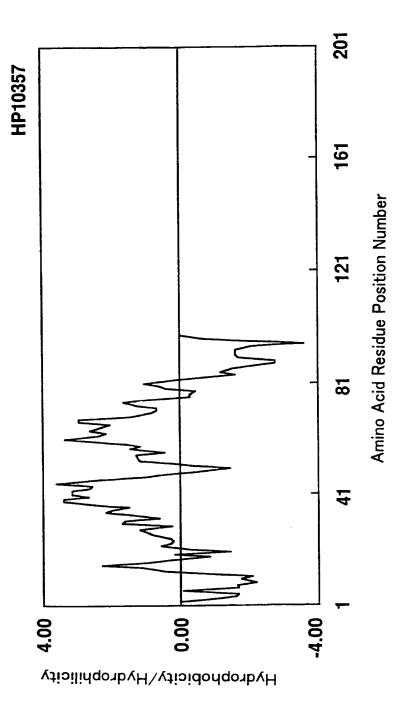


Fig. 14

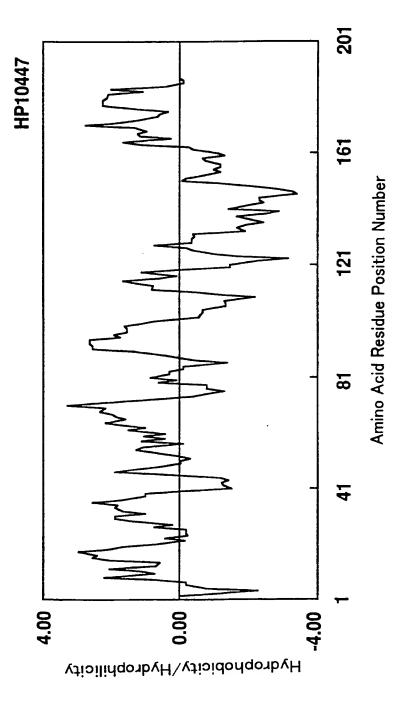


Fig. 15

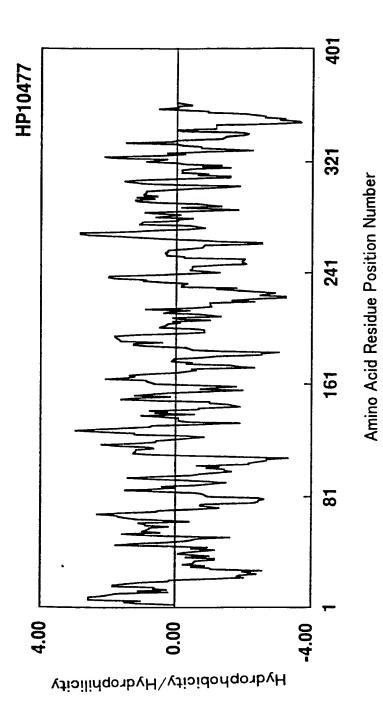


Fig. 16

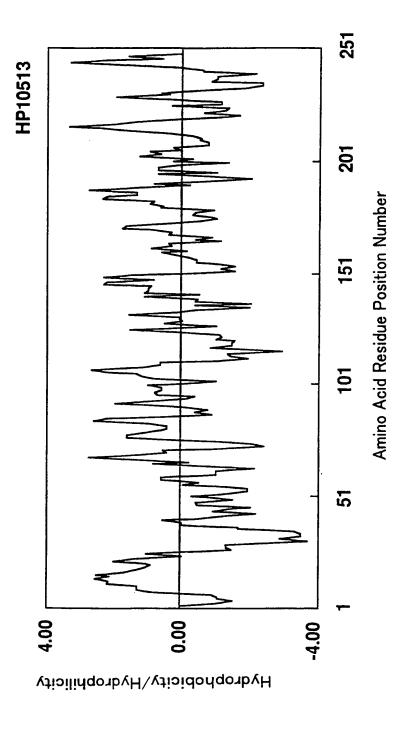


Fig. 17

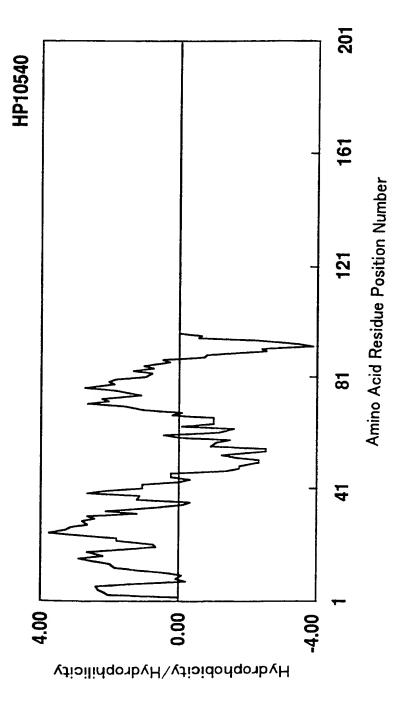


Fig. 18

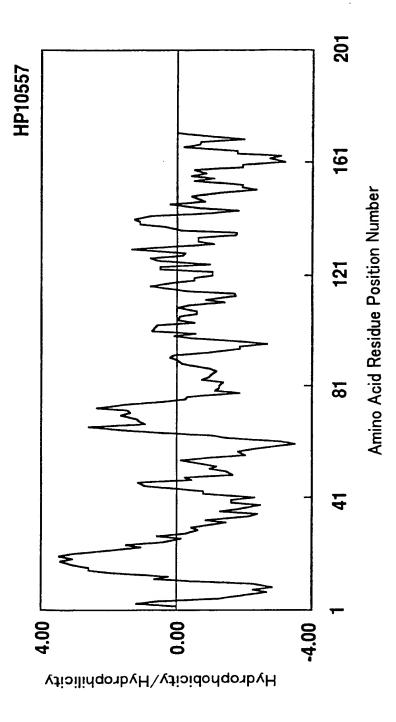


Fig. 19

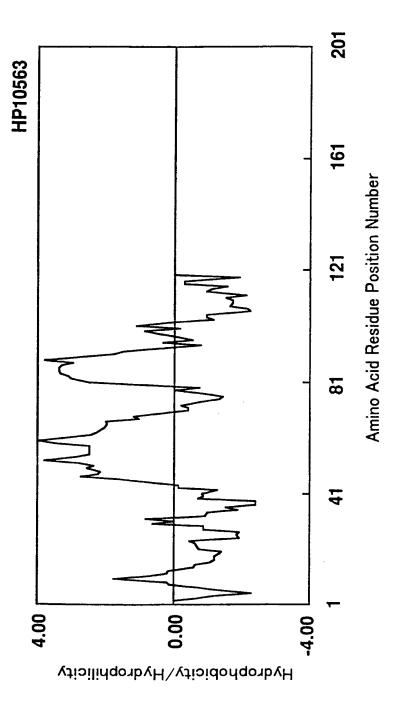


Fig. 20

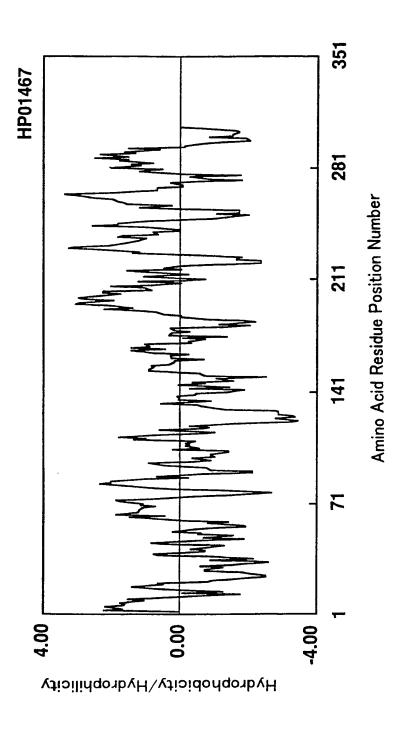


Fig. 21

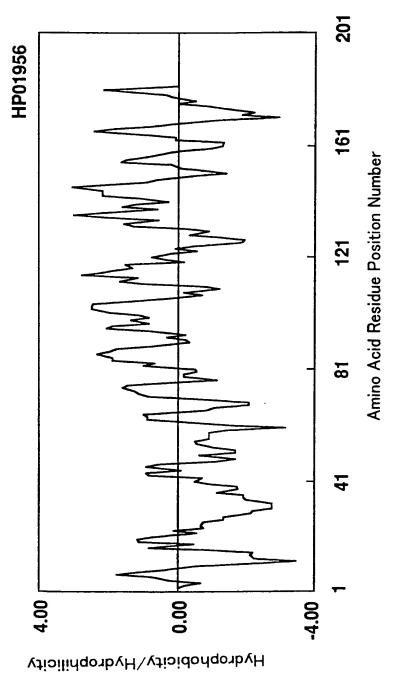


Fig. 22

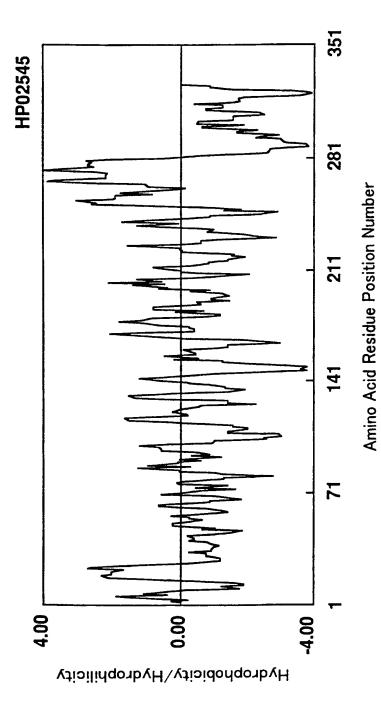


Fig. 23

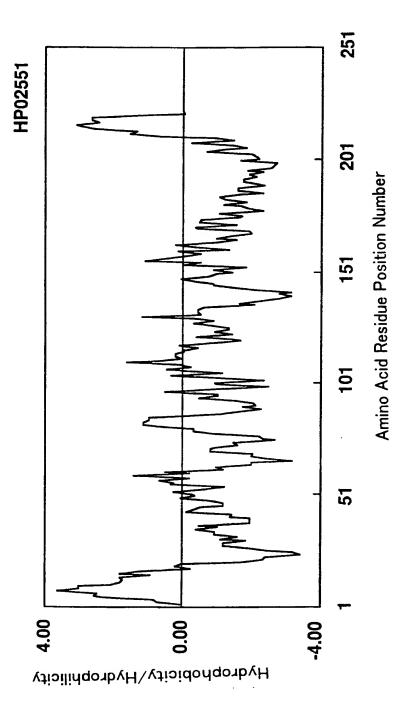


Fig. 24

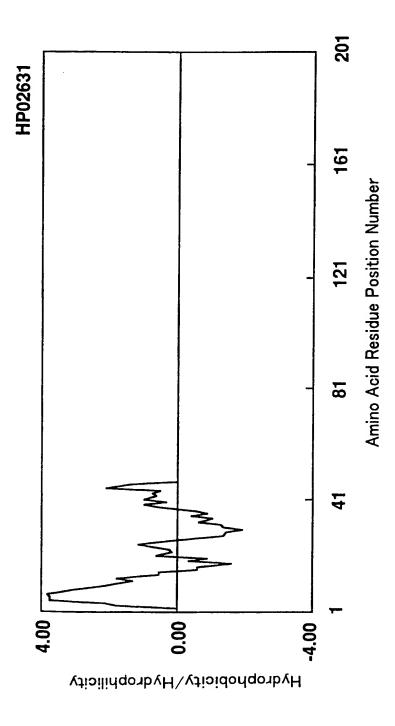


Fig. 25

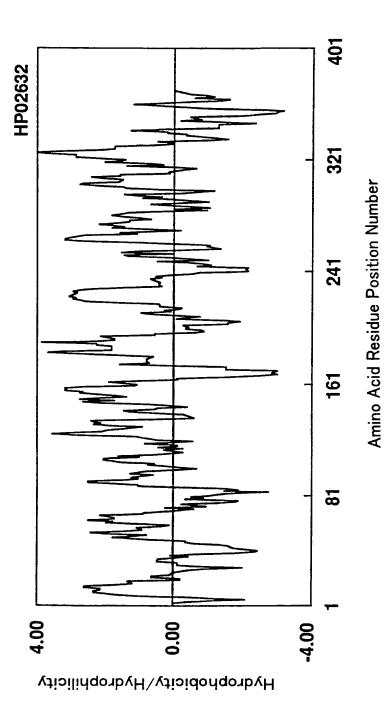


Fig. 26

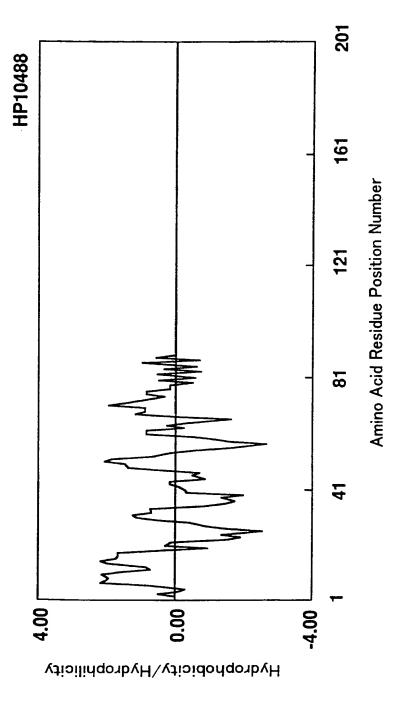


Fig.27

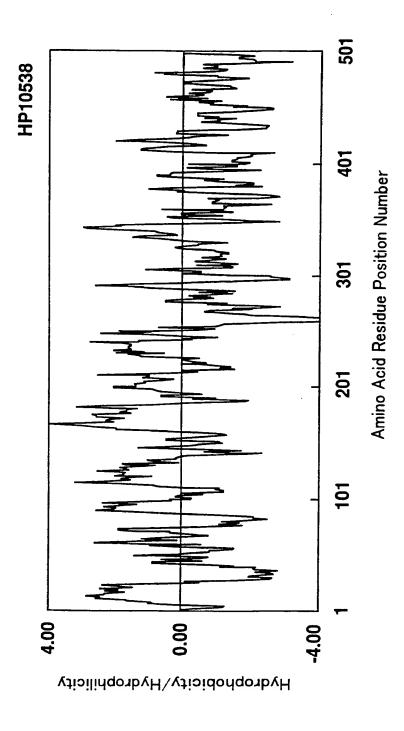


Fig. 28

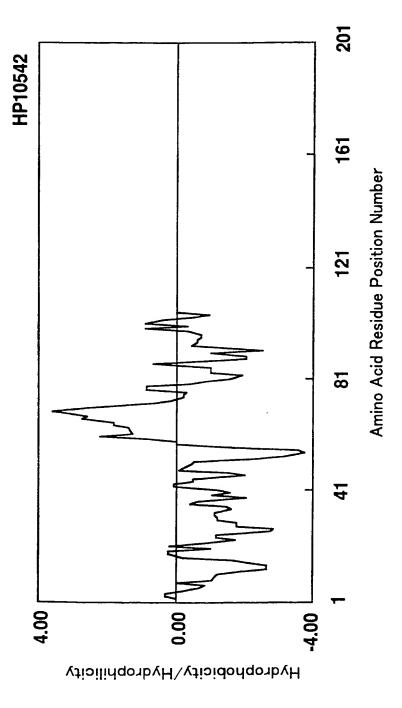


Fig. 29

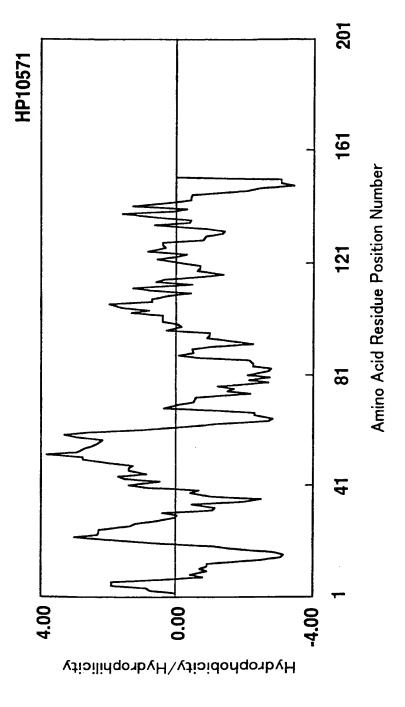


Fig. 30

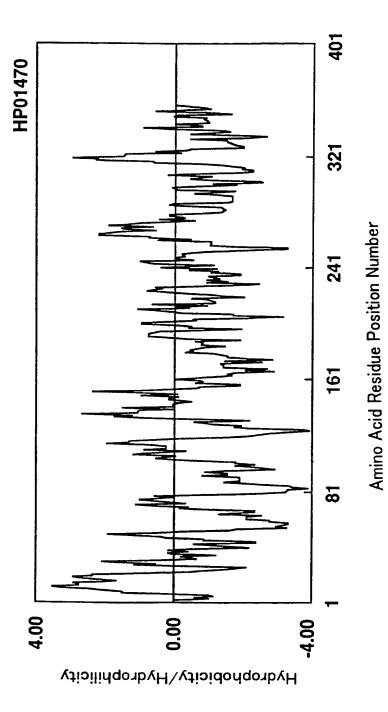


Fig. 31

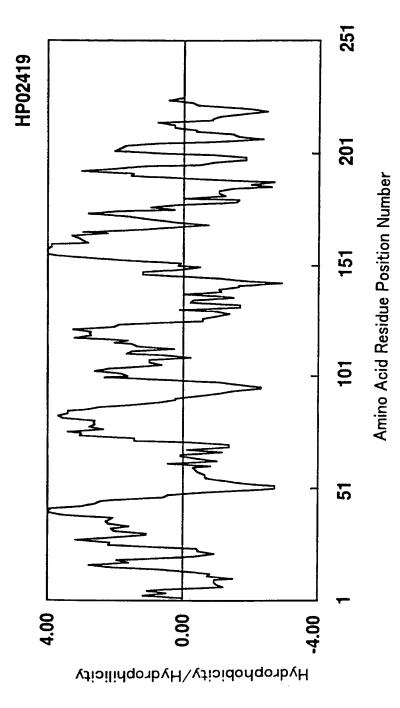
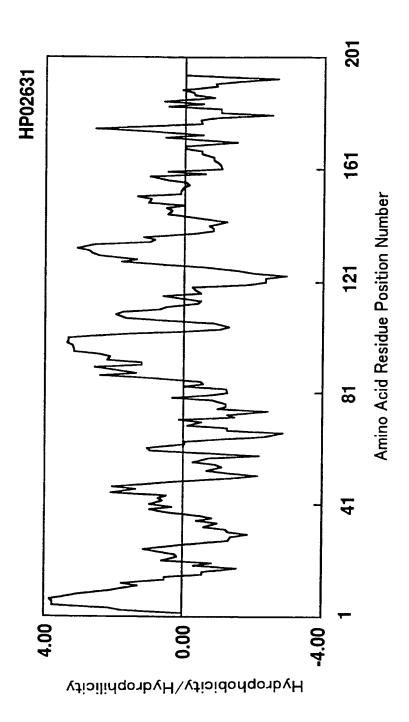


Fig.32



-ig. 33

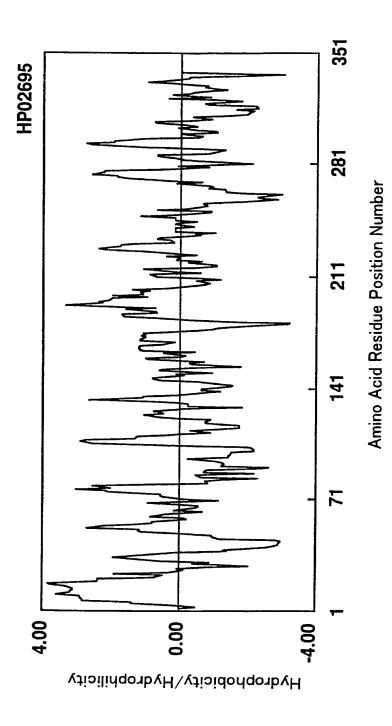


Fig. 34

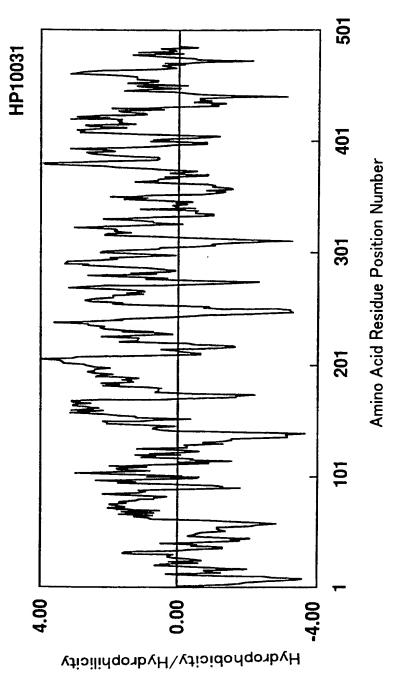


Fig. 35

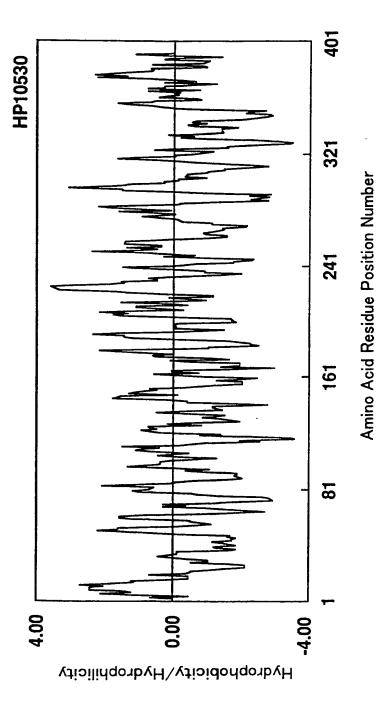


Fig. 36

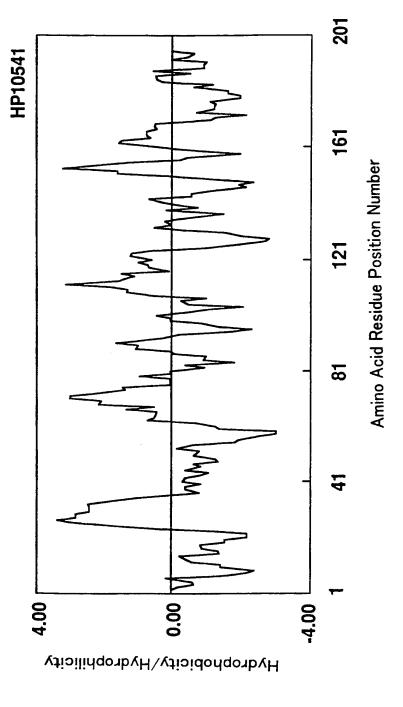


Fig.37

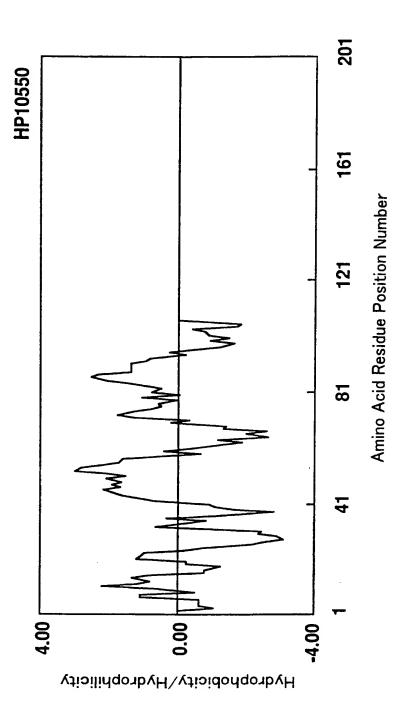


Fig. 38

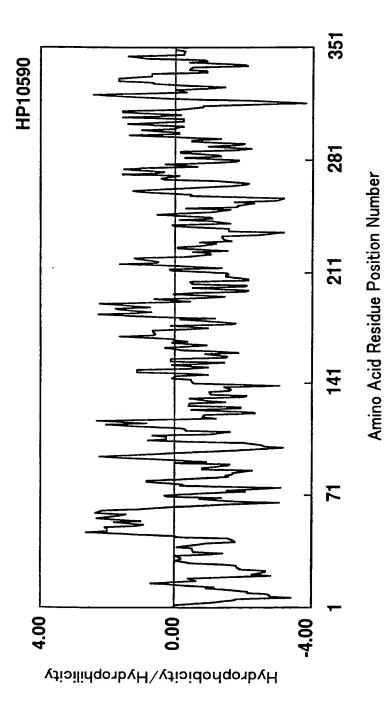


Fig. 39

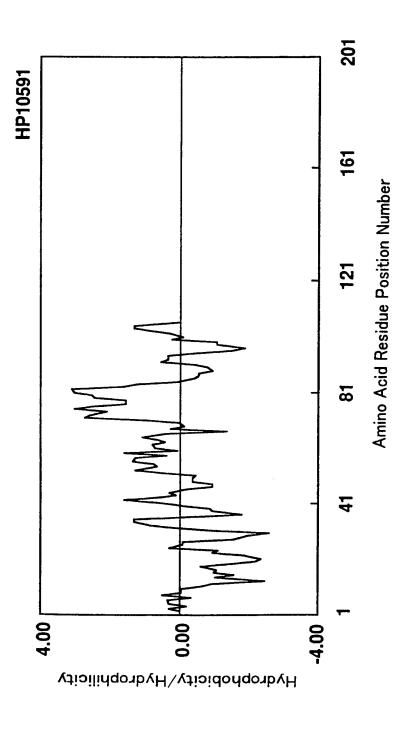


Fig. 40

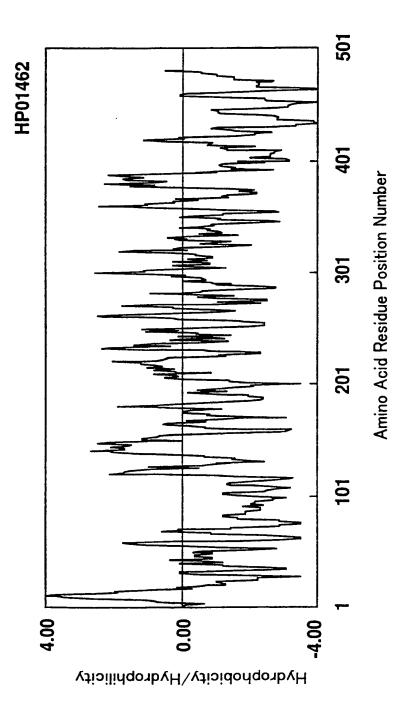
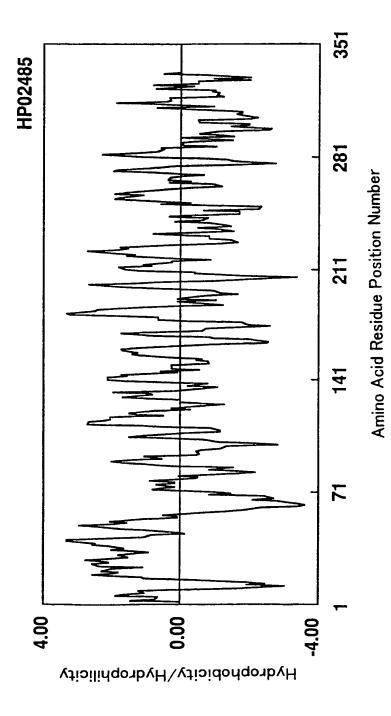


Fig. 41



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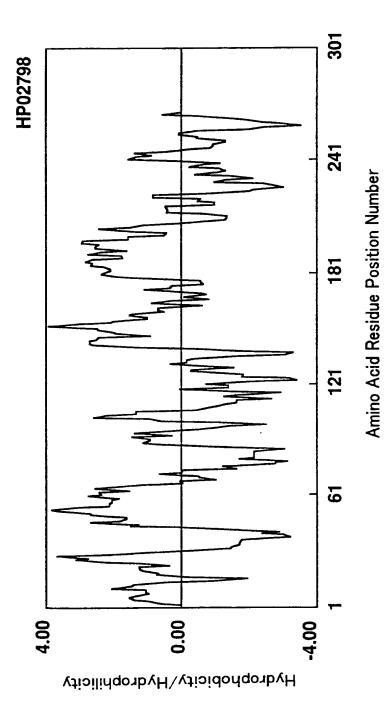


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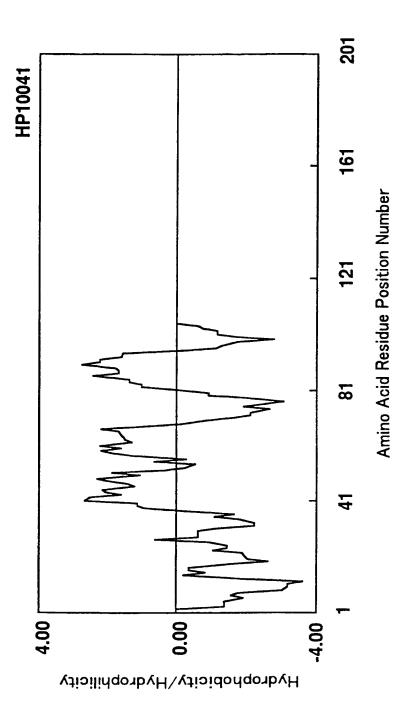


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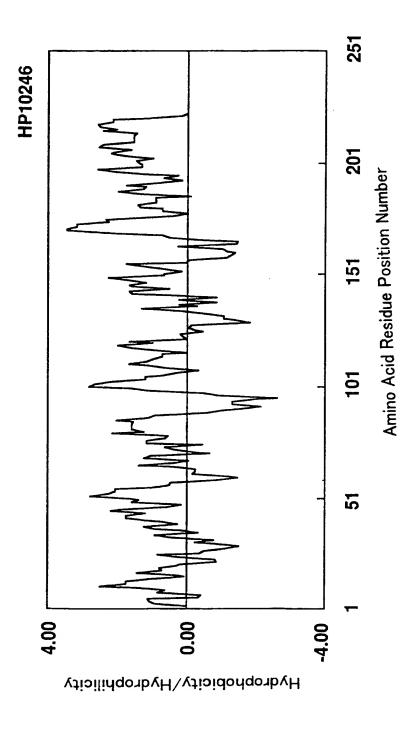


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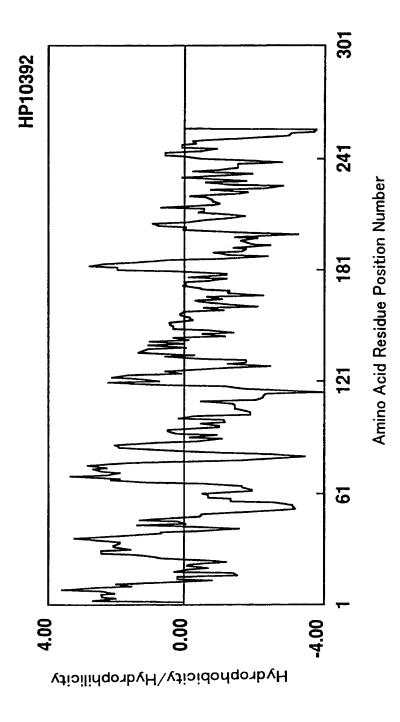


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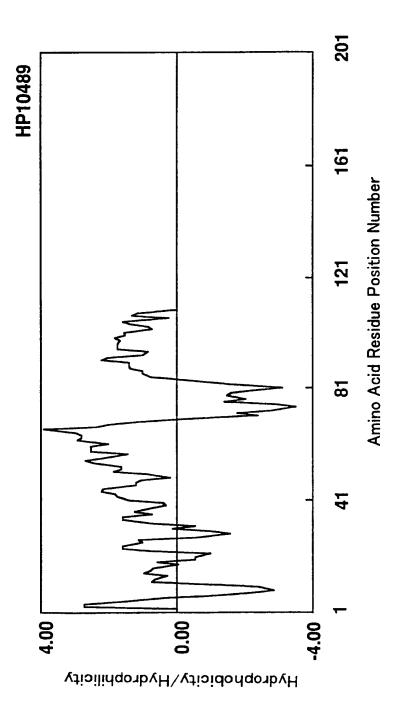


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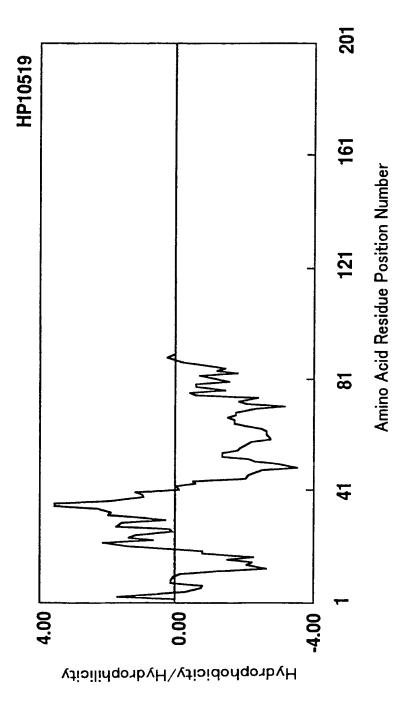


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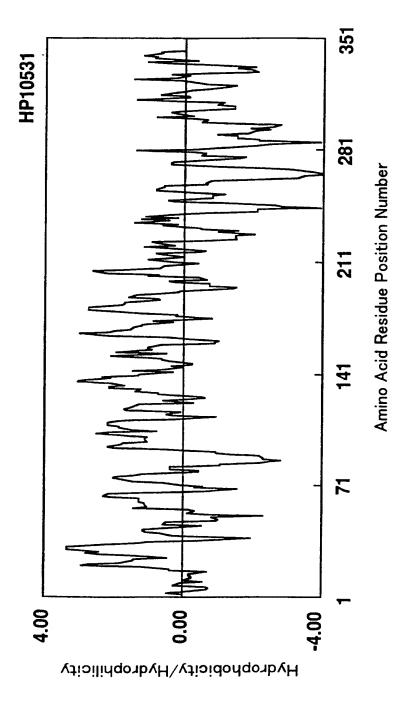


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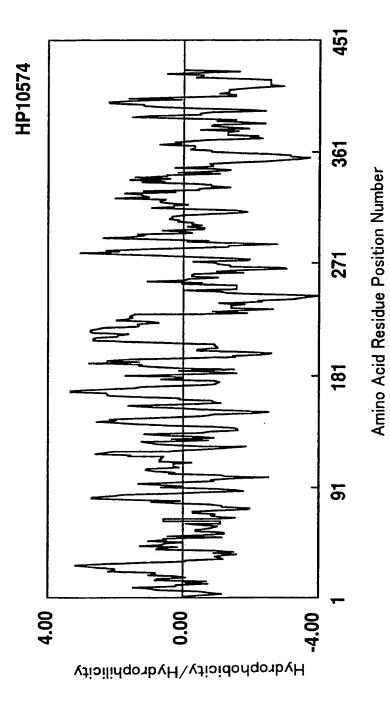


Fig. 50

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																gtctc	1000
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	Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr Val	
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	Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser Pro	
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	Ile Val Val Met Ala Asp Pro Lys Gly Lys Ala Tyr Arg Val Val	
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	Cys Val Ala Leu Ile Phe Ala Cys Leu Val Ile Ile Arg Gln Arg Gln	
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	Met Asp Phe Leu Val Leu Phe Leu	
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	Ser	Lys	Thr	His	Ser	Leu	Lys	Gly	Leu	Ala	Arg	Gly	Gly	Ala	Glr	lle	
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20	105		+		_ 4. 4.	110					115					120	
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	T11T	ASII	PIO	GIY	11e	Ile	Thr	гÀг	Ата		GIU	Leu	Leu	Phe		His	
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	Let	1 Thi	Ala	Sei	Ala	Ala	Thr	· Val	Ala	ıle	val	Ser	Thr	Thr	Phe	e Leu	
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	Asp	Leu	Gly	His	Leu	His	Val	Met	Asp	Thr	Val	Phe	Leu	Ile	Gln	Tyr	
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	Leu	Phe	Leu	Thr	Phe	Pro	Arg	Ile	Val	Phe	Met	Leu	Gly	Phe	Val	Val	
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	Gln	Val	His	Arg	Asn	Ile	His	Ser	His	Gly	Leu .	Arg	Ser	Asn	Leu	Gln	
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	Glu	Ile	Phe	Leu	Pro	Ala	Phe	Pro	Cys	His	Glu /	Arg :	Lys	Lys	Gln	Glu	
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	Met Thr Lys Lys Lys Arg Glu Asn Leu Gly Val Ala Leu Glu Ile Asp	
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	ggg cta gag gag aag ctg tcc cag tgt cgg aga gac ctg gag gcc gtg	157
10	Gly Leu Glu Glu Lys Leu Ser Gln Cys Arg Arg Asp Leu Glu Ala Val	
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	Asn Ser Arg Leu His Ser Arg Glu Leu Ser Pro Glu Ala Arg Arg Ser	
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	Leu Glu Lys Glu Lys Asn Ser Leu Met Asn Lys Ala Ser Asn Tyr Glu	
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	Lys Glu Leu Lys Phe Leu Arg Gln Glu Asn Arg Lys Asn Met Leu Leu	
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	Ser Val Ala Ile Phe Ile Leu Leu Thr Leu Val Tyr Ala Tyr Trp Thr	
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2 5	Met	
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	Met Ala Thr Ser Ser Met Ser Lys Gly Cys Phe																
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	Val :	Phe	Lys	Pro	Asn	Ser	Lys	Lys	Arg	Lys	Ile	Ser	Leu	Pro	Ile	Glu	
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	gac	tat	ttt	aac	aaa	ggg	aaa	aat	gag	cct	gag	gac	agt	aag	ctt	cga	206
	Asp '	Tyr	Phe	Asn	Lys	Gly	Lys	Asn	Glu	Pro	Glu	Asp	Ser	Lys	Leu	Arg	
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	Phe	Glu	Thr	туr	Gln	Leu	Ile	Trp	Gln	Gln	Met	Lys	Ser	Glu	Asn	Glu	
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	Phe :	Leu	Gln	Lys	Ser	His	Ser	Gly	Phe	Gln	Lys	Asn	Ser	Arg	Asp	Leu	
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	Gly	Gly	Gln	Ile	Lys	Leu	Arg	Glu	Ile	Pro	Thr	Ala	Ala	Leu	Val	Leu	
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	Gly	Ile	Tyr	Ala	Tyr	Val	Cys	Ser	Cys	Met	His	Leu	Cys	Val	Phe	Arg	
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	Phe																
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25	_		100					105					110				
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	ту	r Th	r As	n Gl	y Le	u Gl	y Le	u Il	e As	n Le	u Th	r Va	al L	eu 1	Val	Pr	o Pro	
5	130)				13	5				14	0					145	
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	Sei	As:	n Pro	o Le	u Cy	s Se	r Gli	n Se	r Gl	y Gl	n Th	r Se	er Va	al G	ly	Gl	y Ser	
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10	Thr	Ala	a Lei	ı Ar	g Cy:	s Sei	s Sei	Sei	c Glu	ı Gly	y Ala	a Pr	o Ly	s P	ro	Va]	L Tyr	
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	Val	Gln	Asp	Glu	Val	Ser	Gly	Gln	Leu	Ile	Leu	Thi	r As	n L	eu	Ser	Leu	
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		210		-, -		-3-4	215	با تناد .	m 9	J-12		220	y	- y -	1113	311
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225

240

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235

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						act	_										483
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25				tgat	gtto	cec c	ectgo	cagga	ag ca	aggu	crt	g 99ª	agegi	gag			580
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		7722	~~~	+							- a a a	taca	rt aas	add (cete	12 <i>0</i> 002	640
						et ga ag at					-990	tyce	regge	199	بالادر	gageca	673
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	tgggtcc													_		680
	tttcatc															740
0.5	ttattct															800
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	_			20			•		25	-	-		-	30	-	
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	Phe	Pro	Thr	Met	Met	Val	Cys	Met	Met	Ala	Trp	Arg	Pro	Ile	Gln	Ala
				100					105					110		
	Leu	Met		Ile	Ser	Ala	Thr	Phe	Lys	Met	Leu	Glu		Ser	Ser	Gln
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15	Ala	Ser	Asp	Trp		Ala	Phe	Ile	Glu		Pro	Glu	Arg	Met		Phe
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	Phe
115 120 125	Phe
Phe Thr Ile Ile Asn Ser Lys Gln Met Gly Ser Tyr Ser Cys Phe	
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Leu His Gly Lys Asn Lys Pro Leu Ile Ser Tyr Val Gly Asp Ser	Thr
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2 0	63.	.1-	T	20	_	_		~ 1	25	T	T	***	T	30	T	03
	GIU	Ala	Lys	rys	Asn	туг	Tyr		GIN	Lys	Leu	HIS		Leu	гÀг	GIU
	Pho	Bro	35 C***	T	G344	61 -	~1	40	Τ ου	7.00	T	T10	45	C3.,	17-1	17-1
	FIIE	50	Cys	Leu	GIA	GIN		GIY	Leu	Asp	ьys	60	Leu	GIU	vaı	vai
30	Ser		חות	n1-	G3	01 -	55	** - 1	77.	Tlo	mb ~		λαν	C15		Dho
00	65	Asp	Ala	Ата	СТА		GIŸ	var	Ата	тте		СТА	ASII	GIII	THE	
		7 ~~	m	N	m	70	7	77 -	Mc+	т1 ^	75 Dho	770	- ו ת	mh-	1707	80
	noil	ASII	Trp	ASN		PIO	ASN	ATA	Met		rne	WIG	ATG	THE		тте
	Ψh~	m≻~	T 1~	C1	85	C1	7	17m ⁷	77-	90	T 220	mh ~	Dro	~ [ת	95	7 ~~
35	TILL	TIIT	Ile	100	TÀE	отÀ	ASII	val	105	PLO	пλр	TILL	ŁIO	110	ату	nry
UU				IVU					エリコ					1 1 U		

	Leu	Pne	115	val	Pne	Tyr	GIY		Pne	GIA	var	PIO	125	_	Leu	Thi
					_		_	120	_,	~ 1	a 3	3				_
	Trp		ser	Ala	Leu	СТĀ	-	Phe	Pne	GIY	GIY		ATA	ràs	Arg	Let
E	- 3	130	-1	_	_,	_	135					140				
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35	ברא -	A ~~	~ [ת	T ~		n ~~	~ ו ג	865	C1						ر ر	
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	+ 9.0		at a	~ 3~	ata	+ aa		tac	++~	aaa	cta	gcc	taa	cta	tee	ctt	1077
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00		_			_		_	_			=	Val					
	1110	Vul	No.	115	245	Vul	DOI	noc	11.0	250	014	***		m, c	255		
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30		vaı	TTE	Pro	Pro		TTE	Thr	Pro	GIÀ		Asp	GIN	Leu	СТЙ	
30	225	mh	***	•	0 3	230	a 3	a 1	T	n 3 -	235	*** 7	T 011	7 am	~ 3	240
	Pne	THE	HIS	гÀг		Pne	GIU	GIN	Leu		Pro	vai	rea	Asp	-	Pne
	60-	T ~··	Ma±	m} ~	245	2	m	C	m k	250	ui-	C1=	Dro	C1	255	N ===
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, ,	A-1-C	F 1 U	⊥ i⊏U	OCT	111	val	AL 4	Ta	~ y D	* **		* ***				Ly o

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133/177

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	Ser Lys Leu Ile Arg Lys Ala Lys Glu Ala Pro Phe Val Pro Val Gly	
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	Glu	Gln	Leu	Lys	Ser	Phe	Gln	Ile	Ile	Ala	His	Leu	Lys	Arg	Leu	Gln	
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	Asp Leu Thr Leu Arg Ile Gly Arg Leu Val Thr Asp Leu Leu Gln Arg	
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or	_	_	_	100	_		_	1	105	+1 -	**-3	3	*** 1	110	27-	TT: -	
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Cys Arg Glu Cys Arg Arg Cys Val Arg Arg Tyr Asp His His Cys Pro Trp Met Glu Asn Cys Val Gly Glu Arg Asn His Pro Leu Phe Val Val Tyr Leu Ala Leu Gln Leu Val Val Leu Leu Trp Gly Leu Tyr Leu Ala Trp Ser Gly Leu Arg Phe Phe Gln Pro Trp Gly Leu Trp Leu Arg Ser Ser Gly Leu Leu Phe Ala Thr Phe Leu Leu Ser Leu Phe Ser Leu Val Ala Ser Leu Leu Val Ser His Leu Tyr Leu Val Ala Ser Asn Thr Thr Trp Glu Phe Ile Ser Ser His Arg Ile Ala Tyr Leu Arg Gln Arg Pro Ser Asn Pro Phe Asp Arg Gly Leu Thr Arg Asn Leu Ala His Phe Phe Cys Gly Trp Pro Ser Gly Ser Trp Glu Thr Leu Trp Ala Glu Glu Glu Glu Gly Ser Ser Pro Ala Val <210> 124 <211> 106 <212> PRT <213> Homo sapience <400> 124 Met Ser Thr Asn Asn Met Ser Asp Pro Arg Pro Asn Lys Val Leu Arg Tyr Lys Pro Pro Pro Ser Glu Cys Asn Pro Ala Leu Asp Asp Pro Thr Pro Asp Tyr Met Asn Leu Leu Gly Met Ile Phe Ser Met Cys Gly Leu Met Leu Lys Leu Lys Trp Cys Ala Trp Val Ala Val Tyr Cys Ser

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	Tyr	Lys	Ile		Val	Ala	Ala	Leu		Trp	Ala	Thr	Ala		Leu	Ile
	.		_	100		_	_	_	105				-1	110	- 3	_,
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	>	m	115	_		-1		120	_,	_	•		125	a		•• 1
	Asp		гÀг	Tyr	TTE	GIN		ser	ше	Asp	ser		TTE	Ser	Leu	vaı
	*** -	130	- 1-	· · · · · · · · · · · · · · · · · · ·	- 1 -	9	135	a 1	** - 7		.	140	mh	3	(7)	3
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35

75

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Leu Gly Ser Trp Val Leu Ser Ala Leu Phe Asp Phe Leu 100	Leu Ile Glu 110
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230

235

240

35 225

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	Ile	Thr	Leu	Val	Leu	Phe	Leu	His	Asp	Thr	Glu	Leu	Arg	Gln	Trp	Glu	
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	Glu	Arg	Asn	His		Leu	Phe	Val	Val	_	Leu	Ala	Leu	Gln		Val	
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	Gln Pro Trp Gly Leu Trp Leu Arg Ser Ser Gly Leu Leu Phe Ala Thr	
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	Phe Leu Leu Ser Leu Phe Ser Leu Val Ala Ser Leu Leu Val	
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	age eea get gtt tagggttget ggaggeeggg etaeegtett gtgeetga	870
	Ser Pro Ala Val	
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165/177

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	Asn Lys Val Leu Arg Tyr Lys Pro Pro Pro Ser Glu Cys Asn Pro Ala	
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	Leu Asp Asp Pro Thr Pro Asp Tyr Met Asn Leu Leu Gly Met Ile Phe	
	30 35 40	
	age atg tge gge ete atg ett aag etg aag tgg tgt get tgg gte get	192
	Ser Met Cys Gly Leu Met Leu Lys Leu Lys Trp Cys Ala Trp Val Ala	
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	Val Tyr Cys Ser Phe Ile Ser Phe Ala Asn Ser Arg Ser Ser Glu Asp	
	65 70 75	
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20	Thr Lys Gln Met Met Ser Ser Phe Met Leu Ser Ile Ser Ala Val Val	
	80 85 90	
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	Met Ser Tyr Leu Gln Asn Pro Gln Pro Met Thr Pro Pro Trp	
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	tgcccccage tggatagagg gaacetggee ettteetagg gaacaceeta ggettaceee	510
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															1		
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	Ile	Thr	Tyr	Lys	Cys	Ser	Gly	Leu	Ser	Glu	Tyr	Asn	Ala	Phe	Trp	Lys	
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		Val	Gln	Ala	Gly	Val	Thr	Tyr	Leu	Phe	Val	Gln	Leu	Cys	Lys	Met	
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	Pne	11e	Gly		Pne	Met	Lys	Ala		val	Asp	vaı	ATa		Leu	116	
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		100	VUL	MIU	nia	БСС	105		1110			110				JU2	
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	115	•				120		-		_	125				•	130	
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			Ile														
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	cac acc	ttc	cgg (cca c	get q	gtc	ctc	ctg	ctg	atg	ttc	ctc	agt	gtc	tac	644
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	Gly Leu Phe Thr Tyr Val Leu Phe Trp Thr Phe Leu Tyr Gly Met Val	430
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